Harnessing the Phytotherapeutic Treasure Troves of the Ancient Medicinal Plant *Azadirachta indica* (Neem) and Associated Endophytic Microorganisms

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ABSTRACT

Azadirachta indica, commonly known as neem, is an evergreen tree of the tropics and sub-tropics native to the Indian subcontinent with demonstrated ethnomedicinal value and importance in agriculture as well as in the pharmaceutical industry. This ancient medicinal tree, often called the "wonder tree", is regarded as a chemical factory of diverse and complex compounds with a plethora of structural scaffolds that is very difficult to mimic by chemical synthesis. Such multifaceted chemical diversity leads to a fantastic repertoire of functional traits, encompassing a wide variety of biological activity and unique modes of action against specific and generalist pathogens and pests. Until now, more than 400 compounds have been isolated from different parts of neem including important bioactive secondary metabolites such as azadirachtin, nimbidin, nimbin, nimbolide, gedunin, and many more. In addition to its insecticidal property, the plant is also known for antimicrobial, antimalarial, antiviral, anti-inflammatory, analgesic, antipyretic, hypoglycaemic, antiulcer, antifertility, anticarcinogenic, hepatoprotective, antioxidant, anxiolytic, molluscicidal, acaricidal, and antifilarial properties. Notwithstanding the chemical and biological virtuosity of neem, it has also been extensively explored for associated microorganisms, especially a class of mutualists called endophytic microorganisms (or endophytes). More than 30 compounds, including neem "mimetic" compounds, have been reported from endophytes harbored in the neem trees in different ecological niches. In this review, we provide an informative and in-depth overview of the topic that can serve as a point of reference for

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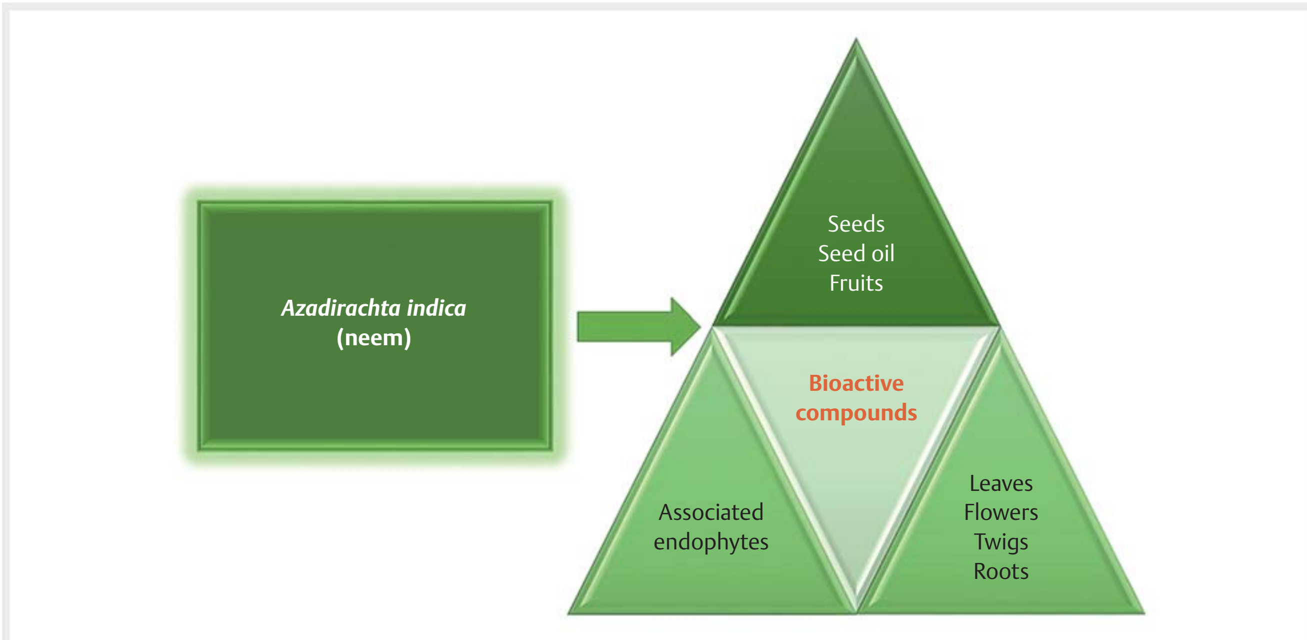
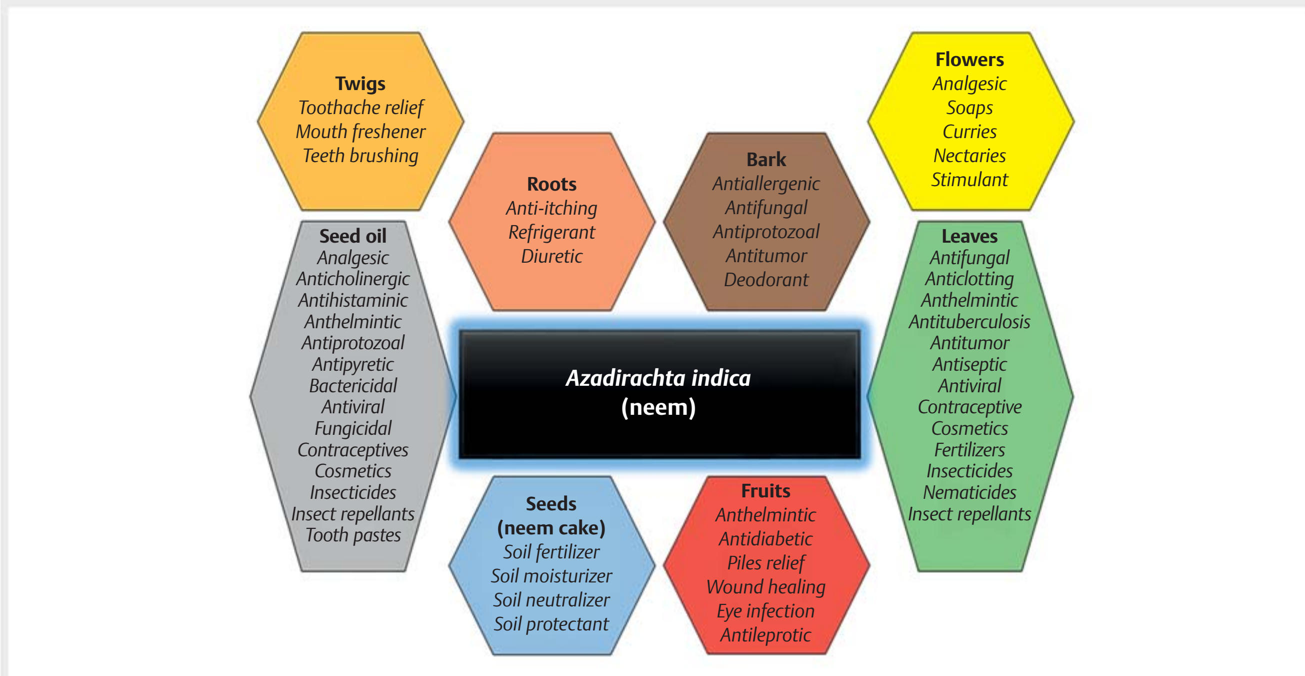
an understanding of the functions and applications of a medicinal plant such as neem, including associated endophytes, within the overall theme of phytopathology. Our review further exemplifies the already-noted current surge of interest in plant and microbial natural products for implications both within the ecological and clinical settings, for a more secure and sustainable future.



Introduction

Neem (*Azadirachta indica* A. Juss.) is native to the Indian subcontinent and is often called a "wonder tree". Considering the importance of neem in agriculture, medicine, industry, and environment, it is colloquially regarded as a tree for solving global problems [1]. India has a long history of using ethnomedicinal plants as traditional medicines (*e.g.*, in Ayurveda, Unani, and Siddha). Neem is a preeminent natural resource containing a vast range of chemically diverse and structurally complex compounds possessing unique biological activities. It is interesting to note that over 400 secondary metabolites of different classes have already been reported from neem prospected from different ecological niches, which certainly justifies its historical use in the traditional medicinal sector ([1] and references therein).

Microbial associations are prevalent in plants; these multifaceted associations range from pathogenic, saprophytic, or opportunistic to more sustained mutualistic interactions such as mycorrhizal and endophytic (fungal, bacterial, and actinobacterial) [2]. Fungi are considered to be one of the most diverse life forms on earth. Although the magnitude of fungal diversity around the world is still open to debate, the estimate of hundreds to thousands of species to even millions has been put forth [2]. The most widely accepted estimate is that of Hawksworth [3] who estimated the size of 1.5 million species, out of which currently over 100 000 species have been discovered. Among the different niches that support the growth of microorganisms, particularly fungi, one unique and specialized habitat is inter- and intracellular spaces of higher plants. These microorganisms are called endophytes. The term "endophyte" was first used by De Bary [4], and the commonly accepted definition pertains to "fungi or bacteria which for all or part of their life cycle, invade the tissues of living plant and cause unapparent and asymptomatic infections entirely within plant tissues, without disease" [5]. Mostert and co-workers (2000) further postulated that "true endophytes are fungi whose colonization never results in visible disease symptoms" [6]. It is now well established that endophytes are capable of maintaining mutualistic associations with their host plants, which often lead to the co-evolution of certain functional traits such as the production of bioactive secondary metabolites. During their co-existence with host plants, endophytes encounter invasion by a plethora of specific and generalist pathogens. Therefore, in order to survive in their ecological niches, endophytes might evolve additional defense strategies such as production of chemical defense compounds, small-molecule chemical modulators for activating host plant defenses, and precursors to host plant secondary metabolites, among others. Thus far, endophytes have emerged as relevant sources of biologically active natural products, and they play an essential role in maintaining the ecological balance in plants. Endophytes harboring neem are, therefore, also an invaluable resource of both novel as well as well-known natural compounds having high and diverse biological functionality for significant medicinal, agricultural, and industrial exploitation [7]. In this review, we provide a detailed elaboration on the metabolites identified to date in the neem plant as well as their biological activities. Further, we discuss thoroughly endophytes reported from neem



▶ **Fig. 1** Important *Azdirachta indica* (neem) plant parts and their uses.

plants and the production of novel, biologically active metabolites.

Neem, the "Wonder Tree"

Neem (*Azadirachta indica* A. Juss.) is an indigenous medicinal plant of the Indian subcontinent [8]. The scientific name of this plant is derived from the Persian word "*Azad dirakhat-I-Hind*" meaning "noble or free tree of India" [9]. Neem had been described as early as 1830 by De Jussieu as an evergreen tree of the tropics and subtropics belonging to the family Meliaceae [10]. Medicinal properties of neem have been inscribed in the ancient testaments of Sanskrit literature as "Arishtha", which translates to "reliever of sickness". Dube (1996) described the ancient Indian names for the neem tree as *prabhadra* (very useful), *paribhadrak* (spreading its utility over vast distances), *sarvobhadrak* (useful in every way), and *rajbhadrak* (best among all the useful trees), all pointing towards its colossal worth in the Indian way of life [11]. Neem is widely used as a folk medicine for various therapeutic purposes as well as a source of agrochemicals for many centuries in the Indian agricultural system. The essential components of neem and their uses are summarized in ▶ **Fig. 1**.

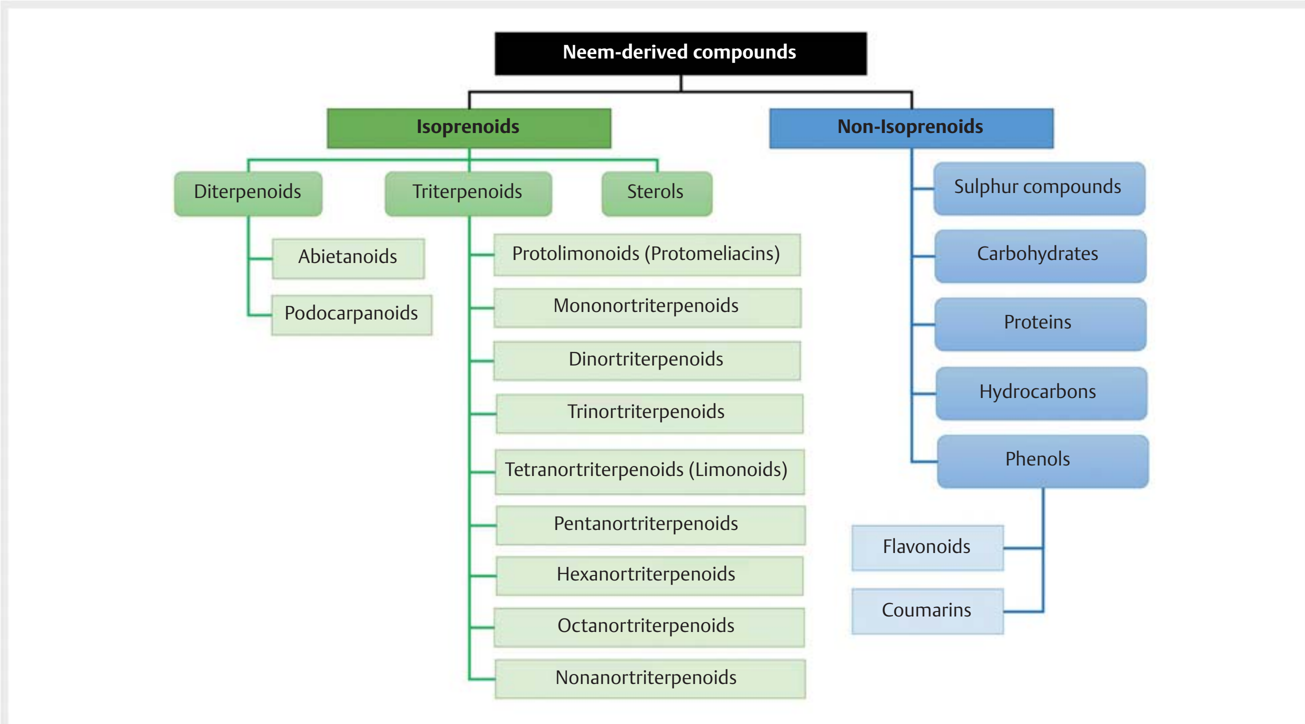
Chemical Diversity of Compounds Reported from Neem

Around 406 compounds have been isolated from different tissues of neem, and several sporadic reviews have also been published on the chemistry and structural diversity of these compounds. The compounds have been divided into 2 major classes: isoprenoids and non-isoprenoids (▶ **Fig. 2**). On the one hand, isoprenoids include diterpenoids and triterpenoids encompassing protomeliacins, limonoids, azadirone, and its derivatives; gedunin and its derivatives; vilasinin type of compounds; and C-secomeliacins such as nimbin, salanin, and azadirachtin. On the other hand, non-isoprenoids are comprised of proteins (amino acids) and carbohydrates (polysaccharides), sulfur compounds, polyphenolics such as flavonoids and their glycosides, dihydrochalcone, coumarin, and tannins including aliphatic compounds, to name a few. The first isolated and characterized compound was nimbin, followed by nimbinin [12, 13]. A considerable assortment of compounds have been isolated from different tissues of neem including leaves, twigs, flowers, fruits, seeds, seeds oil, bark, and roots, which are summarized in ▶ **Table 1** along with their reported biological activities.

Selected Bioactive Principles of Neem and Their Specific Activity

Anti-inflammatory, analgesic, and antipyretic activities

Kaempferol, reported from neem as well as from a different, unrelated plant *Rhamnus procumbens,* was found to have anti-inflammatory and anti-ulcer activities [83, 207]. Anti-inflammatory and immunomodulatory activity was observed in 2 flavonoids, catechin and epi-catechin, reported from the bark of the neem tree [177]. Nimbidin, a major active component of the *Azadirachta indica* seed oil, was found to significantly inhibit some of the functions of macrophages and neutrophils relevant to the inflamma-



▶ **Fig. 2** Chemical classification of *Azdirachta indica* (neem) derived compounds.

tory responses both *in vitro* as well as *in vivo,* signifying anti-inflammatory and anti-arthritic potential of the compound [209]. In another study, the effect of aqueous extract of neem leaves (400 mg/kg body weight) was compared with that of dexamethasone (0.75 mg, intraperitoneal) in rats, which demonstrated statistically significant reduction by extract, albeit less pronounced compared to dexamethasone [210]. Crude ethanol extract of neem leaves yielded anti-inflammatory responses by suppression of paw edema induced by carrageenan and reduced cotton pellet-induced granuloma formation in chronic model rats [211]. Furthermore, the ethanol extract obtained from *A. indica* leaves (1 g/kg w/w) showed significant antinociceptive effect by inhibition of abdominal writhes produced by acetic acid. *A. indica* extract also showed statistically significant antipyretic effect ($p < 0.05$) at 1 g/kg and 500 mg/kg dose level on yeast-induced pyrexia in rats [211].

Immunostimulant activities

Neem oil is shown to selectively activate the cell-mediated immune mechanisms that elicit an enhanced response to subsequent mitogenic or antigenic challenges by acting as a non-specific immunostimulant [212]. Pre-treatment of rats with an odorous and volatile fraction of neem oil, coded NIM-76, was found to increase polymorphonuclear leukocytes, with a decrease in lymphocyte count displaying immunomodulatory efficacy [213].

Radiosensitizing effects

Neem oil was found to increase the radiosensitivity of the Balbc/3 T3 cells and severe combined immunodeficiency (SCID) cells during x-irradiation under aerobic conditions [214]. Application of neem oil reduced the G2 + M phase of the cell cycle, thereby inhibiting the repair of cells from lethal damage [214].

Hypoglycemic activities

Neem kernel powder, in combination with glibenclamide, yielded significant antidiabetic and antihyperlipemic effects in alloxan diabetic rats [215]. Antihyperglycemic effect of aqueous neem leaf extract was also observed in insulin-dependent diabetes mellitus and non-insulin-dependent diabetes mellitus animal models [216]. Mixed water extracts of *Abroma augusta* roots, when combined with the leaves of *A. indica* and given orally to alloxan diabetic rats, showed hypoglycemic action with decreased formation of lipid peroxides estimated as thiobarbituric acid reactive substance along with increased antioxidants in erythrocytes [217]. Extracts of *A. indica* combined with extracts of *Vernonia amygdalina* (Del.) was found to have enhanced anti-diabetic effect in albino Wistar rats [218]. Ethanolic extracts of *A. indica* in streptozotocin-induced hyperglycemia normalized the glucose level and reversed dyslipidemia [219]. Hypoglycemic action of ethanolic neem leaf extract was evaluated in diabetic rats, which demonstrated that after treatment for 24 h with a single dose of 250 mg/kg extract reduced glucose (18%), cholesterol (15%), triglycerides (32%), urea (13%), creatinine (23%), and lipids (15%) [220]. Further, in a multiple-dose study that lasted for 15 days, reduction of creatinine, urea, lipids, triglycerides, and glucose were

▶ **Table 1** Biomolecules reported from different tissues of *Azadirachta indica*.

Sl. No.	Plant tissue	Compounds	Compound class	Biological activity	References
1	Leaves	Quercetin-3-o-β-d-gluco-pyranoside (isoquercitrin)	Flavonoids	n. a.	[14]
2	Leaves	3-hydroxystigmasta-5-en-7-one	Steroids	Antiplatelet aggregation	[15, 16]
3	Leaves	n-Hexacosanol	Miscellaneous compounds	Potent feeding stimulants for larvae of the silkworm	[17, 18]
4	Leaves	Tetratriacontane	Hydrocarbons	n. a.	[19]
5	Leaves	Hexacosene	Hydrocarbons	n. a.	[19, 20]
6	Leaves	β-carotene	Hydrocarbons	n. a.	[21]
7	Leaves	Nimbandiol	Pentanortriterpenoids	Antimalarial activity	[22]
8	Leaves	α-Linolenic acid	Fatty acids and their derivatives	Reduces cardiovascular disease	[23, 24]
9	Leaves	Xanthophylls	Miscellaneous compounds	Antioxidant activities	[20, 21, 25]
10	Leaves	Kaempferol-3-O-rutinoside (or nicotiflorin)	Flavonoids	n. a.	[26]
11	Leaves	Myricetin-3-O-rutinoside	Flavonoids	n. a.	[26]
12	Leaves	Quercetin-3-O-α-L-rhamnoside	Flavonoids	n. a.	[26]
13	Leaves	Quercetin-3-O-rutinoside	Flavonoids	n. a.	[26]
14	Leaves	Quercetrin	Flavonoids	Inhibitors of azoxymethanol-induced colonic neoplasia	[27–31]
15	Leaves	Rutin	Flavonoids	Inhibitors of azoxymethanol-induced colonic neoplasia	[27–29]
16	Leaves	Oxalic acid	Acids and their derivatives	n. a.	[32]
17	Leaves	Ascorbic acid	Acids and their derivatives	n. a.	[32]
18	Leaves	Melianol	Mononotriterpenoids	n. a.	[32]
19	Leaves	2′,3′-dehydrosalannol	Ring-C-seco-tetrano-triterpenoids	n. a.	[33]
20	Leaves	1,3-diacetyl-11,19-deoxo-19-oxomelia-carpin	Ring-C-seco-tetrano-triterpenoids	n. a.	[34]
21	Leaves	Isoazadirolide	Ring-C-seco-tetrano-triterpenoids	n. a.	[35]
22	Leaves	Desfurano-6-α-hydroxy-azadiradione	Octanortriterpenoids	Insecticidal activity against fourth instar larvae of mosquito (*Anopheles stephensi*)	[36]
23	Leaves	22, 23-dihydronimocinol	Tetranortriterpenoids	Insecticidal activity fourth instar larvae of the mosquito (*Anopheles stephensi*)	[36]
24	Leaves	Nimbocinolide	γ-Hydroxybutenolides	n. a.	[37]
25	Leaves	Isonimbocinolide	γ-Hydroxybutenolides	n. a.	[38]
26	Leaves	23-O-methylnimocinolide	γ-Hydroxybutenolides	Insect growth regulating effect on mosquitoes (*Aedes aegypti*)	[39]
27	Leaves	1, 7-O-deacetyl-23-O-methyl-7α-O-senecioylnimocinolide	γ-Hydroxybutenolides	Insect growth regulating effect on mosquitoes (*Aedes aegypti*)	[39]
28	Leaves	Meldenin	Tetranortriterpenoids	Antimalarial activity	[40–42]
29	Leaves	Isomeldenin	Tetranortriterpenoids	Antimalarial activity	[41–43]
30	Leaves	Meldenindiol	Tetranortriterpenoids	n. a.	[41, 43]
31	Leaves	β-sitosterol	Steroids	Insecticidal activity	[20, 44]
32	Leaves	Zafaral	Tetranortriterpenoids	Insect growth regulating against houseflies and toxic on larvae of mosquitoes	[45]

continued

▶ **Table 1** *Continued*

Sl. No.	Plant tissue	Compounds	Compound class	Biological activity	References
33	Fresh leaves	Zeeshanol	Trinortriterpenoids	n. a.	[46]
34	Dried leaves	4α, 6α-dihydroxy-A-homozadirone	Tetranortriterpenoids	n. a.	[47]
35	Air dried leaves	Azadirachtolide	Tetranortriterpenoids	n. a.	[48]
36	Air dried leaves	Deoxyazadirachtolide	Tetranortriterpenoids	n. a.	[48]
37	Air dried leaves	Sulfonoquinovosyldiacyl-glyceride	Glyceride	Antileukemic activity	[49]
38	Fresh leaves	Azadirachtanin	Tetranortriterpenoids	Hyperglycemic activity	[50, 51]
39	Fresh leaves	Nimocinolide	γ-Hydroxybutenolides	Insect growth-regulating properties	[44]
40	Fresh leaves	Isonimocinolide	γ-Hydroxybutenolides	Insect growth- regulating properties	[44]
41	Undried leaves	Nimbocinone	Protolimonoids	n. a.	[51]
42	Leaves extract	Meliacinanhydride	Tetranortriterpenoids	n. a.	[45]
43	Undried winter leaves	Nimocinol (nimonol or 6-hydroxyazadirone)	Tetranortriterpenoids	Antimalarial activity	[42, 52]
44	Fresh green whole leaves	14, 15-epoxynimonol	Tetranortriterpenoids	n. a.	[53]
45	Fresh leaves	Desfurano-desacetylnimbin-17-one	Octanortriterpenoids (ring-C seco-octanortriterpenoids)	n. a.	[54]
46	Chloroform extract of dried leaves	Meliacinolin	Tetranortriterpenoid	Antidiabetic	[55]
47	Methanolic extract of fresh leaves	Odoratone	Protolimonoids	Mortality on fourth instar larvae of mosquitoes (*Anopheles stephensi*)	[56]
48	Methanolic extract of fresh leaves	Meliatetraolenone	Tetranortriterpenoids	Insecticidal activity	[56]
49	Methanolic extract of the fresh leaves	6α-O-acetyl-7-deacetyl-nimocinol	Tetranortriterpenoids	Toxicity on fourth instar larvae of mosquitoes (*Aedes aegypti*)	[57]
50	Methanolic extract of the fresh leaves	Meliacinol	Tetranortriterpenoids	Protection against Tacaribe virus to mice brain	[57]
51	Powdered neem leaves	3-deacetyl-3-cinnamoyl azadirachtin	Ring-C-seco-tetrano-triterpenoids	n. a.	[58]
52	Flower	Neeflone	Tetranortriterpenoid	n. a.	[59]
53	Flower	Flowerone	Flavonoids	n. a.	[60]
54	Flower	Flowerin	Flavonoids	n. a.	[60]
55	Flower	Azharone	Flavonoids	n. a.	[61]
56	Flower	3′-prenylnaringenin	Flavonoids	n. a.	[60]
57	Flower	Trichilenone acetate	Triterpenoid	n. a.	[60]
58	Flower	Prenylated flavanones, 5,7,4′-trihydroxy-8-prenylflavanone	Flavanones	Antimutagenic	[62]
59	Flower	5,4′-dihydroxy-7-methoxy-8-prenylflavanone	Flavanones	Antimutagenic	[62]
60	Flower	5,7,4′-trihydroxy-3′,8-diprenylflavanone	Flavanones	Antimutagenic	[62]
61	Flower	5,7,4′-trihydroxy-3′,5′-diprenylflavanone	Flavanones	Antimutagenic	[62]
62	Flowers	Melicitrin (a glycoside of myricetin)	Flavonoids	n. a.	[63]

continued

▶ **Table 1** *Continued*

Sl. No.	Plant tissue	Compounds	Compound class	Biological activity	References
63	Flowers	Kaempferol-3-glucoside (also called astragalin)	Flavonoids	n. a.	[63]
64	Flowers	Quercetin-3-galactoside (or hyperin)	Flavonoids	n. a.	[63]
65	Flowers	Myricetin-3-arabinoside	Flavonoids	n. a.	[63]
66	Fresh flowers	Diepoxyazadirol	Apo-protolimonoids	n. a.	[60]
67	Fresh flowers	Trichilinone	Tetranortriterpenoids	n. a.	[60]
68	Fresh flowers	O-methylazadironolide	γ-Hydroxybutenolides	n. a.	[60]
69	Fresh flowers	1S,2S,5R-1,4,4-Trimethyl-tricyclo[6.3.1.0 (2,5)]dodec-8-ene	Sesquiterpenoids	n. a.	[64]
70	Fresh flowers	2-Methoxy-5,4′-dimethyl-benzenebutanal	n. a.	n. a.	[64]
71	Fresh flowers	1,4-Dimethoxy-2-(methyl-thio)-benzene	n. a.	n. a.	[64]
72	Fresh flowers	n-Hexadecanoic acid or palmitic acid	n. a.	n. a.	[64]
73	Fresh flowers	Methyl n-hexadecanoate or methyl palmitate	n. a.	n. a.	[64]
74	Fresh flowers	Methyl octadecanoate acid or methyl stearate	n. a.	n. a.	[64]
75	Fresh flowers	Methyl 17-hydroxymethyl-octadecanoate	n. a.	n. a.	[64]
76	Fresh flowers	Decahydro-1,1,3a-trimethyl-7-methylene-[1aS-(1aa′, 3aa′, 7aa′, 7ba′]-1H-cyclopropa[a] naphthalene	Sesquiterpenoids	n. a.	[64]
77	Fresh flowers	1,1,4,8-Tetramethyl-*cis,cis,cis*-4,7,10-cycloundecatriene	Sesquiterpenoids	n. a.	[64]
78	Fresh flowers	Methyl docosanoate or methyl beheniate	n. a.	n. a.	[64]
79	Fresh flowers	Methyl dodecanoate or methyl laurate	n. a.	n. a.	[64]
80	Fresh flowers	Methyl tetradecanoate or methyl myristate	n. a.	n. a.	[64]
81	Fresh flowers	Methyl eicosanoate	Hydrocarbons	n. a.	[64]
82	Fresh flowers	Methyl heptadecanoate	Hydrocarbons	n. a.	[64]
83	Fresh flowers	Methyl hexacosanoate	Hydrocarbons	n. a.	[64]
84	Fresh flowers	Methyl 15-methylhepta-decanoate	Hydrocarbons	n. a.	[64]
85	Fresh flowers	Methyl 14-methylpenta-decanoate	Hydrocarbons	n. a.	[64]
86	Fresh flowers	Methyl 12-methyltridecanoate	Hydrocarbons	n. a.	[64]
87	Fresh flowers	Nonanedioic acid monomethylester	Hydrocarbons	n. a.	[64]
88	Fresh flowers	Methyl octacosanoate	Hydrocarbons	n. a.	[64]
89	Fresh flowers	Methyl 9-oxononaoate	Hydrocarbons	n. a.	[64]
90	Fresh flowers	Methyl 4-oxooctanoate	Hydrocarbons	n. a.	[64]
91	Fresh flowers	Methyl pentacosanoate	Hydrocarbons	n. a.	[64]
92	Fresh flowers	Methyl tetracosanoate	Hydrocarbons	n. a.	[64]
93	Fresh flowers	Methyl 9-methyltetra-decanoate	Hydrocarbons	n. a.	[64]

continued

▸ **Table 1** *Continued*

Sl. No.	Plant tissue	Compounds	Compound class	Biological activity	References
94	Fresh flowers	Methyl 8-(2-furyl)-octanoate	Hydrocarbons	n. a.	[64]
95	Fresh flowers	Germacrene B	Sesquiterpenoids	n. a.	[64]
96	Fresh flowers	*α*-himachalene	Sesquiterpenoids	n. a.	[64]
97	Fresh flowers	*α*-Sitosterol	Steroids	n. a.	[64]
98	Fresh flowers	*α*-Sitosterol acetate	Steroids	n. a.	[64]
99	Fresh flowers	Lanosterol	Steroids	n. a.	[64]
100	Fresh flowers	Tyrosol	Phenolic constituents	n. a.	[60]
101	Fresh flowers	Dodecasanoic acid	Fatty acids and their derivatives	n. a.	[15]
102	Fresh flowers	Heptadecanoic acid or margarnoic acid	Fatty acids and their derivatives	n. a.	[15]
103	Fresh flowers	Hexacosanoic acid or cerotic acid	Fatty acids and their derivatives	n. a.	[15]
104	Fresh flowers	15-methylheptadecanoic acid	Fatty acids and their derivatives	n. a.	[15]
105	Fresh flowers	12-methyltridecanoic acid or isomyristic acid	Fatty acids and their derivatives	n. a.	[15]
106	Fresh flowers	Nonanedioic acid	Fatty acids and their derivatives	n. a.	[64]
107	Fresh flowers	Octacosanoic acid	Fatty acids and their derivatives	n. a.	[15]
108	Fresh flowers	Octadecanoic acid or stearic acid	Fatty acids and their derivatives	n. a.	[64]
109	Fresh flowers	9-oxononaoic acid or azelaldehydic acid	Fatty acids and their derivatives	n. a.	[15]
110	Fresh flowers	4-oxooctanoic acid	Fatty acids and their derivatives	n. a.	[15]
111	Fresh flowers	Pentacosanoic acid	Fatty acids and their derivatives	n. a.	[15]
112	Fresh flowers	9-methyltetradecanoic acid	Fatty acids and their derivatives	n. a.	[15]
	Fresh flowers	17-hydroxysteric acid	Fatty acids and their derivatives	n. a.	[15]
113	Fresh fruits	Melianone	Protolimonoids	Antifeeding activity	[65, 66]
114	Fresh fruits	Nimolinone	Protolimonoids	n. a.	[65, 67]
115	Fresh fruits	Nimocin	Tetranortriterpenoids	n. a.	[44]
116	Fresh fruits	Nimbocinol	Tetranortriterpenoids	Insect growth inhibitory activity	[44, 67]
117	Fresh ripe fruits	Azadirachtol	Apo-protolimonoids	Potent antifeedant	[68–70]
118	Fresh ripe fruits	Azadirachnol (naheedin)	Apo-protolimonoids	n. a.	[71]
119	Fresh ripe fruits	Azadirol	Apo-protolimonoids	n. a.	[72]
120	Fruits	17-epi-Azadiradione	Tetranortriterpenoids	n. a.	[73]
121	Fruits	17-*β* -hydroxyazadiradione	Tetranortriterpenoids	Antifeedant activities and growth inhibitor activity against larvae of rice leaf folder	[73, 74]
122	Fruits	Nimbocetin	Acids and their derivatives	n. a.	[31]
123	Fruits	5-hydroxymethylfurfural	Miscellaneous compounds	n. a.	[31]
124	Fruits	Ochinolide B	Ring-C-seco-tetrano-triterpenoids	n. a.	[75, 76]
125	Fruits	Nimbochalcin	Coumarin and chalcones	n. a.	[31]
126	Fresh fruit coats	Azadironic acid	Tetranortriterpenoids	Toxic against mosquito (*Anopheles stephensi*)	[77, 78]
127	Fresh fruit coats	Limocinin	Tetranortriterpenoids	n. a.	[79]
128	Fresh fruit coats	Limocin-A	Tetranortriterpenoids	Insecticidal activity	[77, 79]
129	Fresh fruit coats	Limocin-B	Tetranortriterpenoids	Insecticidal activity	[77, 79]
130	Fresh fruit coats	Limocin-C	Tetranortriterpenoids	n. a.	[80]
131	Fresh fruit coats	Limocin-D	Tetranortriterpenoids	n. a.	[80]

continued

▸ **Table 1** *Continued*

Sl. No.	Plant tissue	Compounds	Compound class	Biological activity	References
132	Fresh fruit coats	Meliacinolactol	Trinortriterpene	n. a.	[80]
133	Fresh undried ripe fruits	Nimolicinolic acid	Hexanortriterpenoids	n. a.	[81]
134	Fresh fruit coats	Desfuranoazadiradione	Octanortriterpenoids	Insect growth regulating activity	[77, 82]
135	Fresh fruit coatings	Galoxolide or 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethyl-cyclopenta[g]-2-benzopyran	n. a.	n. a.	[17, 83]
136	Fresh fruit coatings	Methyl 14-methyl-pentadecanoate	n. a.	n. a.	[83]
137	Fresh fruit coatings	2,6-bis(1,1-dimethylethyl)-4-methyl phenol	n. a.	n. a.	[83]
138	Fresh fruit coatings	2-(phenylmethylene)-octanal or α-hexylcinnamaldehyde	n. a.	n. a.	[83]
139	Fresh fruit coatings	Ethyl hexadecanoate or ethyl palmitate	n. a.	n. a.	[83]
140	Fresh fruit coatings	Ethyl 9Z-octadecenoate or ethyl oleate	n. a.	n. a.	[83]
141	Fresh fruit coatings	Methyl 14-methyl pentadecanoate	n. a.	n. a.	[83]
142	Fresh fruit coatings	3,7-dimethyl-1-octen-7-ol or dihydromyrcenol	n. a.	n. a.	[83]
143	Fresh fruit	Azadironol	Octanortriterpenoids	n. a.	[77, 84]
144	Fruit coat extract	Meliacinin	Dinortriterpenoids	Toxic against mosquito (*Anopheles stephensi*)	[77, 78]
145	Fresh fruit coats	Salimuzzalin	Tetranortriterpenoids	n. a.	[40, 84]
146	Fruit coatings	Limocinol	Protolimonoids	n. a.	[79]
147	Fruit coatings	Limocinone	Protolimonoids	n. a.	[79]
148	Fruit coatings	Kulactone	Protolimonoids	n. a.	[72]
149	Fruit coats	Methyl (2E, 6E)-farnesoate or Methyl-3,7,11-trimethyl-2E,6E,10-dodecatrienoate	Sesquiterpenoids	n. a.	[17, 83]
150	Fruit coats	Dihydromyreenol	Monoterpenoids	n. a.	[17]
151	Fruit coats	T-butylated hydroxytoluene	Phenolic constituents	n. a.	[17]
152	Fruit coats	α-hexyl cinnamaldehyde	Phenolic constituents	n. a.	[17]
153	Fruit coats	β-asarone	Phenolic constituents	Antifungal activity	[17, 83, 85]
154	Fruit coats	Azadirolic acid	Dinortriterpenoids	n. a.	[84]
155	Fruit coats	Azadiradionol	Dinortriterpenoids	n. a.	[84]
156	Fruit coats	Azadironolide	γ-Hydroxybutenolides	n. a.	[86]
157	Fruit coats	Isoazadirodionolide	γ-Hydroxybutenolides	n. a.	[86]
158	Fruit coats	Azadiradionolide	γ-Hydroxybutenolides	n. a.	[86]
159	Fruit coats	Icosane	Hydrocarbons	n. a.	[71]
160	Fruit coats	Docosane	Hydrocarbons	n. a.	[71]
161	Fruit coats	2-methyltricosane	Hydrocarbons	n. a.	[71]
162	Fruit coats	Docosene	Hydrocarbons	n. a.	[71]
163	Fruit coats	n-pentadecane	Hydrocarbons	n. a.	[83]
164	Fruit coats	n-hexadecane	Hydrocarbons	n. a.	[83]
165	Fruit coats	n-heptadecane	Hydrocarbons	n. a.	[83]
166	Fruit coats	n-tetracosane	Hydrocarbons	n. a.	[83]
167	Fruit coats	n-hexacosane	Hydrocarbons	n. a.	[83]

continued

▶ **Table 1** *Continued*

Sl. No.	Plant tissue	Compounds	Compound class	Biological activity	References
168	Fresh, undried, and unruptured ripe fruits	Isonimolicinolide	Tetranortriterpenoids	n. a.	[81]
169	Seeds	Vepaol	Ring-C-seco-tetrano-triterpenoids	n. a.	[58, 87, 88]
170	Seeds	Isovepaol	Ring-C-seco-tetrano-triterpenoids	n. a.	[88, 89]
171	Seeds	Indole acetic acid	Acids and their derivatives	Plant growth hormone	[90]
172	Seeds	Indole pyruvic acid	Acids and their derivatives	n. a.	[90]
173	Seeds	Tiglic acid	Acids and their derivatives	n. a.	[90]
174	Seeds	7-deacetylazadiradione	Tetranortriterpenoids	n. a.	[91]
175	Seeds	Epoxyazadiradione	Tetranortriterpenoids	Insecticidal activity, anti-inflammatory activity	[71, 91, 92]
176	Seeds	7-acetylneotrichilenone	Tetranortriterpenoids	n. a.	[91]
177	Seeds	7-benzoyl-17-hydroxy-nimbocinol	Tetranortriterpenoids	n. a.	[93]
178	Seeds	15-hydroxyazadiradione	Tetranortriterpenoids	n. a.	[93]
179	Seeds	23-deoxyazadironolide	γ-Hydroxybutenolides	n. a.	[93]
180	Seeds	Limocin E	Tetranortriterpenoids	n. a.	[93]
181	Seeds	23-epilimocin E	Tetranortriterpenoids	n. a.	[93]
182	Seeds	7a-acetoxy-3-oxoisocopala-1,13-dien-15-oic acid	Diterpenoid	n. a.	[93]
183	Dried seeds	1α-methoxy-1, 2-dihydro-nimbinin	Tetranortriterpenoids	n. a.	[91]
184	Dried seeds	1β, 2β-diepoxyazadiradione	Tetranortriterpenoids	n. a.	[91]
185	Seed oil	1α, 2α-epoxy-17β-hydroxy-azadiradione	Tetranortriterpenoids	n. a.	[94]
186	Seed oil	Vepinin	Tetranortriterpenoids	n. a.	[95]
187	Seed oil	Mahmoodin	Tetranortriterpenoids	Effective against human pathogenic bacteria	[71, 96]
188	Seed oil	1α, 2α-epoxynimolicinol	Tetranortriterpenoids	n. a.	[94]
189	Seed oil	7-deacetylnimolicinol	Tetranortriterpenoids	n. a.	[94]
190	Seed oil	Vilasinin triacetate	Tetranortriterpenoids	n. a.	[43]
191	Seed oil	1-*O*-senecioyl-3-*O*-acetylvilasinin	Tetranortriterpenoids	n. a.	[97]
192	Seed Oil	Di-, tri- and tetra- sulfides	Sulphur containing compounds	n. a.	[98, 99]
193	Seed oil	Gedunin	Tetranortriterpenoids (meliacins/limonoids)	Antifeedant activities and growth inhibitor activity against larvae of rice leaffolder, *In vitro* cytotoxic activities	[71, 74, 100, 101]
194	Seed oil	7-decacetylgedunin	Tetranortriterpenoids	Antifeedant activities and growth inhibitor activity against larvae of rice leaffolder	[74, 100]
195	Seed Oil	Nimolicinol	Tetranortriterpenoids	Antibacterial to several human pathogenic bacteria	[52, 94, 96]
196	Seed oil	17-epi-Nimbocinol	Tetranortriterpenoids	n. a.	[102]
197	Neem oil	Methyl esters of 14-methyl-pentadecanoic acid	Fatty acids and their derivatives	n. a.	[17]
198	Neem oil	Methyl esters of ethyl palmate	Fatty acids and their derivatives	n. a.	[17]
199	Neem oil	Methyl esters of oleate	Fatty acids and their derivatives	n. a.	[17]

continued

▸ **Table 1** *Continued*

Sl. No.	Plant tissue	Compounds	Compound class	Biological activity	References
200	Neem oil	Salannin	Ring-C-seco-tetrano-triterpenoids	Antifeeding properties	[76, 103–106]
201	Neem oil	3-deacetylsalannin	Ring-C-seco-tetrano-triterpenoids	Antifeeding properties	[22, 104, 107]
202	Neem oil	Salannol	Ring-C-seco-tetrano-triterpenoids	Antifeeding properties	[22]
203	Neem oil	Salannol acetate	Ring-C-seco-tetrano-triterpenoids	Antifeeding properties	[108]
204	Neem oil	Campesterol	Steroids	Cholesterol lowering anticarcinogenic and angiogenesis activity	[109, 110]
205	Neem oil	Sitosterol	Steroids	Anthelminthic and antimutagenic activities	[109, 111]
206	Neem oil	Fucosterol	Steroids	Cytotoxicity against breast and colon carcinoma cell line	[109, 112]
207	Neem oil	9-octadecanoic acid-hexa-decanoic acid-tetrahydro-furan-3,4-diyl ester	Fatty acids and their derivatives	Antibacterial	[113]
208	Seed extract	7-decacetyl-7-benzoylgedunin	Tetranortriterpenoids	Cytotoxic activity against HL60 leukemia cells	[91, 114]
209	Seed extract	7-desacetyl-7- benzoyl-epoxyazadiradione	Tetranortriterpenoids	Cytotoxic activity against HL60 leukemia cells	[91, 114]
210	Seeds	Vilasinin	Tetranortriterpenoids		[22, 43]
211	Seeds	1, 3-di-O-acetylvilasinin	Tetranortriterpenoids	Insect antifeeding activity	[22]
212	Seeds	1-O-tigloyl-3-O-acetylvilasinin	Tetranortriterpenoids	Insect antifeeding activity	[115]
213	Seeds	Limbocinin	Tetranortriterpenoids	n. a.	[116]
214	Seeds	Limbocidin	Tetranortriterpenoids	n. a.	[117]
215	Seeds	4-epi-nimbin	Ring-C-seco-tetrano-triterpenoids	n. a.	[117]
216	Seeds	6-deacetylnimbinal	Ring-C-seco-tetrano-triterpenoids	n. a.	[118]
217	Seeds	Nimbanal (nimbinal)	Ring-C-seco-tetrano-triterpenoids	n. a.	[108, 118]
218	Seeds	Nimbinol	Ring-C-seco-tetrano-triterpenoids	n. a.	[118]
219	Seeds	Nimbolide	Ring-C-seco-tetrano-triterpenoids	Cytotoxic activities against N1E-115 murine neuro-blastoma cells, anticancerous activity against human breast cancer cells	[107, 119–122]
220	Seeds	28-deoxonimbolide	Ring-C-seco-tetrano-triterpenoids	Cytotoxic activities against HL60 cells	[114, 118, 123]
221	Seeds	Ochinin acetate (ochinin-3-acetate)	Ring-C-seco-tetrano-triterpenoids	n. a.	[124]
222	Seeds	Azadirachtin	Ring-C-seco-tetrano-triterpenoids	Most potent insect antifeedant and insect growth-regulating agent	[125, 126]
223	Seeds	2′,3′-dihydrotigloyl-azadirachtol	Tetranotriterpenoids	n. a.	[127]
224	Seeds	3-isobutyrylazadirachtol	Tetranotriterpenoids	n. a.	[127]
225	Seed extract	Azadirachtin G	Ring-C-seco-tetrano-triterpenoids	n. a.	[128, 129]

continued

▶ **Table 1** *Continued*

Sl. No.	Plant tissue	Compounds	Compound class	Biological activity	References
226	Seed extract	3-O-acetyl-1-O-hydroxy-azadirachtol	Tetranotriterpenoids	n. a.	[128, 129]
227	Seeds	11α-hydroxy-12-norazadirachtin	Tetranotriterpenoids	n. a.	[130]
228	Seeds	Azadirachtin D	Ring-C-seco-tetrano-triterpenoids	n. a.	[128, 131, 132]
229	Seeds	Azadirachtin I	Ring-C-seco-tetrano-triterpenoids	n. a.	[128, 131, 133]
230	Seeds	Azadirachtin F	Ring-C-seco-tetrano-triterpenoids	n. a.	[128, 131, 132]
231	Seeds	1-O-Tigloyl-3-O-acetyl-11-hydroxymeliacarpinin	Tetranortriterpenoids	n. a.	[97]
232	Seeds	11 β-hydroxy-azadirachtinin	Tetranotriterpenoids	n. a.	[15]
233	Seeds	7-benzoylnimbocinol	Limonoid	Cytotoxic activity	[114]
234	Seeds	17-epiazadiradione	Limonoid	n. a.	[114]
235	Seeds	17-epi-17-hydroxy-azadiradione	Limonoid	n. a.	[114]
236	Seeds	1,3-diacetylvilasinin	Tetranortriterpenoids	n. a.	[114]
237	Seeds	7-deacetylgedunin	Tetranortriterpenoids	n. a.	[114]
238	Seeds	6-deacetylnimbin	Limonoid	n. a.	[114]
239	Seeds	20,30-dihydrosalannin	Limonoid	n. a.	[114]
240	Seed oil	Salannolide	Ring-C-seco-tetrano-triterpenoids	n. a.	[134]
241	Seed extract	1-O-acetyl-7-O-tigloylvilasinin	Tetranortriterpenoids	n. a.	[115]
242	Dried seeds	1-O-Tigloyl-3-O-acetyl-12α-acetoxyvilasinin	Tetranortriterpenoids	n. a.	[97, 135]
243	Dried seeds	1–3-di-O-acetyl-12α-acetoxyvilasinin	Tetranortriterpenoids	n. a.	[97, 135]
244	Dried seeds	7-O-Tigloyl-12α-acetoxyvilasinin	Tetranortriterpenoids	n. a.	[97, 135]
245	Seeds	1-O-acetyl-7-O-tigloyl-nimbidinin	Tetranortriterpenoids	n. a.	[97, 135]
246	Seeds	1, 3-di-O-acetyl-7-O-tigloyl-12β -hydroxyvilasinin	Tetranortriterpenoids	n. a.	[136]
247	Seeds	3-O-acetyl-7-O-tigloylvilasinin lactone	Tetranortriterpenoids	n. a.	[137]
248	Seeds	Azadirachtin K	Ring-C-seco-tetrano-triterpenoids	n. a.	[138]
249	Seed	3-deacetyl-11-desoxy-azadirachtin	Ring-C-seco-tetrano-triterpenoids	n. a.	[137]
250	Seeds	11-hydroxyazadirachtin B	Ring-C-seco-tetrano-triterpenoids	n. a.	[136]
251	Seeds	23-desmethyllimocin-B	Limonoids	n. a.	[136]
252	Seeds	1-tigloyl-3-acetyl-azadirachtinin	Ring-C-seco-tetrano-triterpenoids	n. a.	[136]
253	Seeds	1,2-diacetyl-7-tigloyl-12-hydroxyvilasinin	Tetranortriterpenoids	n. a.	[136]
254	Seeds	11-epi-azadirachtin H	Ring-C-seco-tetrano-triterpenoids	n. a.	[139]
255	Seeds	4α-benzoylnimbandiol	Pentanortriterpenoids	n. a.	[76]

continued

▶ **Table 1** *Continued*

Sl. No.	Plant tissue	Compounds	Compound class	Biological activity	References
256	Seeds	1-Tigloyl-3-acetyl-11-hydroxy-4β-methylmeliacarpin (11-epi-azadirachtin D)	Terpenoids	n. a.	[140, 141]
257	Seeds	1α-destigloyl-1α-benzoyl-azadirachtin	Ring-C-seco-tetrano-triterpenoids	n. a.	[76]
258	Oil, seeds	Glyceride of α-Linolenic acid	Fatty acids and their derivatives	n. a.	[32]
259	Seed kernels	Nimbidic acid	Ring-C-seco-tetrano-triterpenoids	n. a.	[142, 143]
260	Seed kernels	1, 2-dihydro-4α, 6α-dihydroxy-A-homozadirone	Tetranortriterpenoids	n. a.	[15, 144]
261	Seed kernels	Nimbin	Tetranortriterpenoids (meliacins/limonoids)	Insecticidal activity	[12]
262	Seed kernels	Azadirachtin M	Ring-C-seco-tetrano-triterpenoids	n. a.	[145]
263	Seed kernels	Azadirachtin N	Ring-C-seco-tetrano-triterpenoids	n. a.	[145]
264	Seed kernels	Azadirachtin B (3-tigloyl-azadirachtol)	Tetranotriterpenoids	Insect growth regulating properties	[58, 146–149]
265	Seed kernels	Nimbidinin	Tetranortriterpenoids	n. a.	[142, 143]
266	Neem kernel	13,14-desepoxyazadirachtin-A	Tetranortriterpenoid, ring-C-seco-tetranotriterpenoids	n. a.	[150]
267	Seed kernels	Salannolactam-21	Nitrogen containing Limonoids	Antifeedant activity	[151]
268	Seed kernels	Salannolactam-23	Nitrogen containing Limonoids	Antifeedant activity	[151]
269	Seed kernels	Azadirachtin H	Ring-C-seco-tetrano-triterpenoids	Insect antifeedant and ecdysis-inhibiting activity	[131–133]
270	Neem kernel extract	Limbonin	Trinortriterpenoids	n. a.	[152, 153]
271	Methanolic extract of air-dried kernels	1-benzoyl-3-deacetyl-1-detigloyl salannin	Limonoids	n. a.	[154]
272	Methanolic extract of air-dried kernels	7-tigloyl-12-oxo vilasini	Limonoids	n. a.	[154]
273	Methanolic extract of air-dried kernels	Azadiralactone	Limonoids	n. a.	[154]
274	Methanolic extract of air-dried kernels	Azadirahemiacetal	Triterpenoid	n. a.	[154]
275	Seed oil	Nimbinene	Pentanortriterpenoids	n. a.	[22]
276	Seed oil	6-deacetylnimbinene	Pentanortriterpenoids	n. a.	[22]
277	Seed oil	6-O-acetylnimbandiol	Pentanortriterpenoids	n. a.	[22, 105]
278	Fresh twigs	6,8-dihydroxy-3-methyl-3,4-dihydroisocoumarin	Coumarin and chalcones	n. a.	[15]
279	Twigs	7,8-dihydroxy-3-methyl-3,4-dihydroisocoumarin	Coumarin and chalcones	n. a.	[15]
280	Twigs	Margocetin (3,4-dihydroxy-7–8-dimethoxy-3-methyl-isocoumarin)	Coumarin and chalcones	n. a.	[15]
281	Fresh twigs	6-methoxymellein (3,4-dihydroxy-6-methoxy-3-methylisocoumarin)	Coumarin and chalcones	Inhibits the growth of several fungi, yeasts and bacteria	[15, 155, 156]
282	Twigs	Isofraxidin (7-hydroxy-6-8-dimethoxycoumarin)	Coumarin and chalcones	Cytotoxic activity	[15, 157]

continued

▶ **Table 1** *Continued*

Sl. No.	Plant tissue	Compounds	Compound class	Biological activity	References
283	Twigs	Isonimolide	γ-Hydroxybutenolides	n. a.	[158]
284	Twigs	Isonimbolide	γ-Hydroxybutenolides	n. a.	[158]
285	Twigs	Methyl esters of eicosenoic acid	Fatty acids and their derivatives	n. a.	[17]
286	Twigs	Margosinolide	Ring-C-seco-tetrano-triterpenoids	n. a.	[159]
287	Twigs	Isomargosinolide	Ring-C-seco-tetrano-triterpenoids	n. a.	[159]
288	Twigs	6-deacetylnimbinolide	Ring-C-seco-tetrano-triterpenoids	n. a.	[160]
289	Twigs	6-deacetyl-isonimbinolide	Ring-C-seco-tetrano-triterpenoids	n. a.	[160]
290	Stem bark	1-O-Tigloyl-3-O-acetyl-11-methoxyazadirachtinin	Tetranotriterpenoids	n. a.	[97]
291	Powdered bark	22,23-dihydro-23β -methoxy-azadirachtin	Tetranotriterpenoids	n. a.	[58]
292	Stem bark	Nimbosodione	Diterpenoids	n. a.	[161]
293	Stem bark	Nimbisonol	Diterpenoids	n. a.	[161]
294	Stem bark	Demethylnimbionol	Diterpenoids	n. a.	[161]
295	Stem bark	Isomargolonone	Diterpenoids	n. a.	[162]
296	Stem bark	Margolone	Diterpenoids	n. a.	[162]
297	Stem bark	Margolonone	Diterpenoids	n. a.	[162]
298	Stem bark	Margosolone	Diterpenoids	n. a.	[163]
299	Stem bark	Margosone	Diterpenoids	n. a.	[163]
300	Stem bark	Methylnimbiol	Diterpenoids	n. a.	[164]
301	Stem bark	Nimbosone	Diterpenoids	n. a.	[164]
302	Stem bark	Nimosone	Diterpenoids	n. a.	[164]
303	Stem bark	Methylnimbionone	Diterpenoids	n. a.	[164]
304	Stem bark	Nimbione	Diterpenoids	n. a.	[165]
305	Stem bark	Nimbinone	Diterpenoids	n. a.	[165]
306	Stem bark	Nimbionol	Diterpenoids	n. a.	[166]
307	Stem bark	Nimbionone	Diterpenoids	n. a.	[166]
308	Stem bark	Nimbonolone	Diterpenoids	n. a.	[167]
309	Stem bark	Nimbonone	Diterpenoids	n. a.	[167]
310	Stem bark	Nimbiol	Diterpenoids	n. a.	[168–171]
311	Stem bark	Sugiol (7-oxoferruginol)	Diterpenoids	Anti-inflammatory activity	[168–172]
312	Stem bark	Margosinone	Polyacetates	n. a.	[173]
313	Stem bark	Margosinolone	Polyacetates	n. a.	[173]
314	Heart Wood	24-methylene-lophenol	Steroids	n. a.	[174]
315	Trunk wood	1,3-di-O-acetyl-7-O-cinna-moylvilasinin (nimbolin A)	Tetranortriterpenoids	n. a.	[175]
316	Trunk wood	Nimbolin B	Ring-C-seco-tetrano-triterpenoids	Insect antifeeding activity	[175, 176]
317	Bark	Gallocatechin	Flavonoids	n. a.	[177]
318	Bark	epi-catechin	Flavonoids	Anti-inflammatory and immunomodulatory	[177]
319	Bark	Catechin	Flavonoids	Anti-inflammatory and immunomodulatory	[177]
320	Bark	epi-gallocatechin	Flavonoids	Antioxidant activity	[177, 178]
321	Bark	Gallic acid	Acids and their derivatives	n. a.	[177]

continued

▸ **Table 1** *Continued*

Sl. No.	Plant tissue	Compounds	Compound class	Biological activity	References
322	Bark	Fraxinellone	n. a.	Antimutagenic activity	[175, 179]
323	Bark	4,14α-dimethyl-5α-ergosta-8,24(28)-diene-3β-ol	Steroids	n. a.	[180]
324	Bark	4α-methyl-5α-ergosta-8,24(28)-diene-3β-ol	Steroids	n. a.	[180]
325	Stem bark	Methyl grevillate	Acids and their derivatives	n. a.	[167]
326	Stem bark	Isonimbinolide	Ring-C-seco-tetrano-triterpenoids	Antifeedant activity	[165, 181]
327	Root bark	Azadiricin	Diterpenoids	n. a.	[182]
328	Root bark	Azadirilin	Diterpenoids	n. a.	[182]
329	Root bark	Azadirin A	Diterpenoids	n. a.	[182]
330	Root bark	Azadirin B	Diterpenoids	n. a.	[182]
331	Root bark	Nimbocinin	Diterpenoids	n. a.	[182]
332	Root bark	Nimbolicidin	Ring-C-seco-tetrano-triterpenoid	n. a.	[182]
333	Root bark	Nimbocin	Hexanortriterpenoids	n. a.	[182]
334	Roots	Azadirinin	Tetranortriterpenoids	n. a.	[183]
335	Root bark	Margocilin	Diterpenoids	n. a.	[184]
336	Root bark	Margocin	Diterpenoids	n. a.	[184]
337	Root bark	Margocinin	Diterpenoids	n. a.	[184]
338	Root bark	Nimbidiol	Diterpenoids	n. a.	[185]
339	Root bark	Nimbilicin	Diterpenoids	n. a.	[182]
340	Root bark	Nimbocidin	Diterpenoids	n. a.	[182]
341	Root bark	Nimolinin	Diterpenoids	n. a.	[182]
342	Root bark	Nimbilin	Ring-C-seco-tetrano-triterpenoids	n. a.	[182]
343	Wood oil	Cycloeucalenol	Triterpenes	n. a.	[186]
344	Wood oil	24-methylenecycloartanol	Triterpenes	n. a.	[186, 187]
345	Gum exudate	D-glucose	Carbohydrates and proteins	n. a.	[188]
346	Gum exudate	D-glucoronic acid	Carbohydrates and proteins	n. a.	[188]
347	Gum exudate	L-arabinose	Carbohydrates and proteins	n. a.	[188]
348	Gum exudate	L-fucose	Carbohydrates and proteins	n. a.	[188]
349	Gum exudate	Mannose	Carbohydrates and proteins	n. a.	[189]
350	Gum exudate	Xylose	Carbohydrates and proteins	n. a.	[189]
351	Gum exudate	Rhamnose	Carbohydrates and proteins	n. a.	[189]
352	Gum exudate	D-glucosamine	Carbohydrates and proteins	n. a.	[190]
353	Gum exudate	Aldobiouronic acid	Carbohydrates and proteins	n. a.	[191]
354	Gum exudate	4-O-(4-O-methyl-α-D-glucopyranosyl uronic acid)-D-galactose	Carbohydrates and proteins	n. a.	[191]
355	Gum exudate	Aldotriouronic acid	Carbohydrates and proteins	n. a.	[191]
356	Fruit coat-ex-tract, Seed oil	Epoxyazadiradione (nimbinin),	Tetranortriterpenoids (meliacins/limonoids)	Insecticidal activity	[78, 192]
357	Fruit coat-ex-tract, Seed oil	Azadiradione	Tetranortriterpenoids (meliacins/limonoids)	Insecticidal activity	[78, 100]
358	Seeds and leaves	1-O-cinnamoylvilasinin lactone	Tetranortriterpenoids	n. a.	[135]
359	Seeds and leaves	1-O-tigloyl-3-O-acetylvilasinin lactol	Tetranortriterpenoids	n. a.	[135]

continued

▸ **Table 1** *Continued*

Sl. No.	Plant tissue	Compounds	Compound class	Biological activity	References
360	Seeds and leaves	1-O-senecioyl-3-O-acetyl-vilasinin lactone	Tetranortriterpenoids	n. a.	[193]
361	Seeds and leaves	1-O-senecioyl-3-O-acetyl-vilasinin lactol	Tetranortriterpenoids	n. a.	[193]
362	Twigs and seed kernels; seed extracts	6-deactylnimbin	Ring-C-seco-tetrano-triterpenoids	Anti-feeding properties	[106, 160, 194]
363	Branches and leaves	4 α-hydroperoxy-6- O-acetylnimbandiol	Triterpenoids	n. a.	[121]
364	Branches and leaves	24,25-epoxy-3 β -hydroxy-20-oxo-7-tirucallene	Triterpenoids	n. a.	[121]
365	Branches and leaves	22,23;24,25-diepoxy-3 β -hydroxy-7-tirucallene	Triterpenoids	n. a.	[121]
366	Fresh fruit coats and seeds	5α-androsta (13β Me)-7α-acetoxy-17-oxo-4,4,8-trimethyl-1,14-dien-3,16-dione (β -nimolactone)	Nonnanortriterpenoids	n. a.	[82, 93]
367	Fresh fruit coats and seeds	5α-androsta (13α Me)-7α-acetoxy-17-oxo-4,4,8-trimethyl-1,14-dien-3,16-dione (α-nimolactone)	Nonnanortriterpenoids	n. a.	[82, 93]
368	Neem oil	Cholesterol	Steroids	n. a.	[195]
369	Neem oil	Stigmasterol	Steroids	n. a.	[195]
370	Fruit coats, Flowers	Hentriacontane	Hydrocarbons	Anti-inflammatory activity	[19, 20, 64, 83, 196]
371	Aqueous extracts of powdered neem leaf, flowers	Azadirone	Tetranortriterpenoids (meliacins/limonoids)	Cytotoxic activity against a panel of human cancer cell	[47, 197, 198]
372	Leaves, oil	Meliantriol	Protolimonoids	n. a.	[199]
373	Leaves and flower	Nimbaflavone	Flavonoids	n. a.	[61, 200]
374	Neem oil and fresh fruit coatings	3,4-dihydro-4,4,5,8-tetramethylcoumarin	Coumarin and chalcones	n. a.	[17, 83]
375	Neem oil and fresh fruit coatings	3,4-dihydro-4,4,7,8-tetra-methyl-coumarin-6-ol	Coumarin and chalcones	n. a.	[17, 83]
376	Leaves and twigs	Scopoletin (7-Hydroxy-6-methoxycoumarin)	Coumarin and chalcones	Antithyroid and antihyper-glycemic activity	[35, 201]
377	Leaves, fruit coats	Octadecane	Hydrocarbons	n. a.	[19, 20, 83]
378	Leaves, fruit coats, flowers	Nonadecane	Hydrocarbons	n. a.	[19, 20, 64, 83]
379	Fruit coats, flowers	Isoazadironolide	γ-Hydroxybutenolides	n. a.	[61, 86]
380	Fruit coats; fresh flowers	Pentacosane	Hydrocarbons	n. a.	[64, 83]
381	Leaves, flowers, fruit coats	Nonacosane	Hydrocarbons	n. a.	[19, 20, 64, 83]
382	Fruit coats; fresh flowers	Heptacosane	Hydrocarbons	n. a.	[19, 20, 64, 83]
383	Fruit coats; fresh flowers	Octacosane	Hydrocarbons	n. a.	[19, 20, 64, 83]

continued

▸ **Table 1** *Continued*

Sl. No.	Plant tissue	Compounds	Compound class	Biological activity	References
384	Fruit coats; flowers	Heneicosane	Hydrocarbons	n. a.	[64, 83]
385	Fruit coats, flowers	Tricosane	Hydrocarbons	n. a.	[64, 83]
386	Oil, seeds, leaves, twigs and fruits	Glycerides and methyl esters of oleic acids	Fatty acids and their derivatives	n. a.	[202, 203]
387	Oil, seeds, leaves, twigs and fruits	Glycerides and methyl esters of stearic acids	Fatty acids and their derivatives	n. a.	[202, 203]
388	Oil, seeds, leaves, twigs and fruits	Glycerides and methyl esters of palmitic acids	Fatty acids and their derivatives	n. a.	[202, 203]
389	Oil, leaves, twigs and fruits	Glycerides and methyl esters of myristic acids	Fatty acids and their derivatives	n. a.	[202, 203]
390	Oil, leaves and twigs	Glycerides and methyl esters of arachidic acids	Fatty acids and their derivatives	n. a.	[202, 203]
391	Oil and leaves	Glycerides and methyl esters of behenic acids	Fatty acids and their derivatives	n. a.	[202, 203]
392	Oil and leaves	Glycerides and methyl esters of lignocernoic acids	Fatty acids and their derivatives	n. a.	[202, 203]
393	Leaves and twigs	Methyl esters of hexadeca-trienoic acid	Fatty acids and their derivatives	n. a.	[17]
394	Leaves and twigs	Methyl esters of lauric acid	Fatty acids and their derivatives	n. a.	[17]
395	Oil/leaves	3-Deacetylazadirachtin	Ring-C-seco-tetrano-triterpenoids	n. a.	[97, 204]
396	Oil/leaves	2′,3′-dihydrotigloyl-azadirachtin	Ring-C-seco-tetrano-triterpenoids	n. a.	[97]
397	Oil/leaves	1-detigloyl-1-isobutyl-roylazadirachtin	Ring-C-seco-tetrano-triterpenoids	n. a.	[97]
398	Oil/leaves	1-detigloyl-1-isovaleroyl-Azadirachtin	Ring-C-seco-tetrano-triterpenoids	n. a.	[97]
399	Oil/leaves	1-detigloyl-1-isocaproyl-3-epoxymethacroy azadirachtin	Ring-C-seco-tetrano-triterpenoids	n. a.	[97]
400	Oil/leaves	β-D-glucoside	Steroids	n. a.	[205]
401	Oil/leaves	Margocidin	Steroids	n. a.	[182]
402	Oil/leaves	Isorhamnetin	Flavonoids	*In vitro* antitumor activity	[15, 30, 206]
403	Oil/leaves	Kaempferol	Flavonoids	Anti-inflammatory and anti-ulcer effects	[88, 207]
404	Oil/leaves	Myricetin	Flavonoids	Antioxidant activity	[88, 208]
405	Oil/leaves	Nimbilicidin	n. a.	n. a.	[182]

n. a.: not available

observed [221]. In the year 2012, a new tetranortriterpenoid named meliacinolin was isolated from chloroform extract of dried neem leaves, which demonstrated *in vivo* inhibition of α-glucosidase and α-amylase enzyme activities in streptozotocin-nicotinamide-induced type 2 diabetes in mice [55]. Inhibition of both these enzymes offers an effective strategy of lowering the levels of postprandial hyperglycemia that prevents the digestion of carbohydrates, offering promising potential of meliacinolin as an antidiabetic agent [55].

Anti-ulcer effects

The aqueous leaf extract of neem showed anti-ulcer properties in stressed rats by preventing mast cell deregulation and increasing the amount of adherent gastric mucus [221]. Neem leaf extract exhibited anti-ulcer activity on gastric lesions in rats by blocking acid secretion through inhibition of H^+-K^+-ATPase and by preventing oxidative damage and apoptosis [222].

Antifertility effects

Prolonged antifertility effects were observed by a single intrauterine administration of neem oil in female Wistar rats [223]. In another study, a single dose of 50 µl of neem oil on each side of the lumen of the vas deferens of male Wistar rats acted as a long-term male contraception [224]. The neem oil fraction NIM-76 was shown to have spermicidal activity *in vivo* not only in rats but also in rabbits and rhesus monkeys; NIM-76 was further found to affect the motility of sperm leading to the observed infertility [225, 226]. Aqueous extract of old and tender neem leaf was found to immobilize and kill 100 % human spermatozoa within 20 s [227].

Antimalarial activities

Gedunin, a tetranortriterpenoid isolated from neem, was reported to be active against *Plasmodium falciparum*, the causative organism of malaria [228]. The antimalarial activity of the limonoids (meldenin, isomeldenin, nimocinol, and nimbandiol) isolated from the ethanolic extract of fresh neem tree was reported to be active against chloroquine-resistant *P. falciparum* strain K1 [229]. Schwikkard and van Heerden (2002) discussed the antimalarial activity of neem compounds such as the limonoid gedunin, meldenin, and azadirachtin [230]. NeemAzal, a commercial neem seed extract containing the limonoid azadirachtin as the main component, was found to block the activity of rodent malarial parasite, *Plasmodium berghei*, in its vector *Anopheles stephensi* [231].

Antiretroviral activities

An acetone-water extract of neem leaves was found to prevent the invasion of human lymphocytes by human immunodeficiency virus (HIV), thereby protecting the target cells without any adverse effects [232]. The acetone-water extract significantly increased CD4 cell count in HIV I or HIV II patients that also led to a substantial increase in mean body weight, hemoglobin concentration, lymphocyte differential count with no adverse effects, and abnormalities in kidney and liver function parameters [233].

Antifungal activities

Khan and Shah (1992) tested leaf extracts of *A. indica* on wheat seed mycoflora and noted considerable reduction in seed mycoflora vis-à-vis better seed germination [234]. Suresh et al. (1997) studied the antifungal activity of polar extract and the impure HPLC fractions of green leaves of *A. indica* against groundnut rust disease (causal agent *Puccinia arachidis* Speg.) [235]. Govindachari et al. (1998) also showed the synergistic effect of various neem terpenoids on different fungal pathogens [236]. Minimum inhibitory concentration (MIC) of neem seed extract was found to be 31 µg/ml against clinical isolates of dermatophytes (*Trichophyton rubrum, Trichophyton mentagrophytes*, and *Microsporum nanum*) [237]. Wang et al. (2010) reported a significant reduction in the growth of the pathogens *Monilinia fructicola, Penicillium expansum, Trichothecium roseum*, and *Alternaria alternata* by neem seed kernel extracts [238].

Antibacterial activities

Mahmoodin, a novel limonoid, isolated from neem oil, showed significant antibacterial activity against various Gram-positive and Gram-negative bacteria [71]. Aquaneem, an emulsified product prepared from the neem kernel, exhibited antibacterial activity against *Aeromonas hydrophila* and *Pseudomonas fluorescens* as well as *Myxobacteria* sp., which are pathogenic to fish [239]. Moreover, SaiRam and co-workers (2000) studied the antimicrobial activity of the extract NIM-76 against certain bacteria, fungi, and Poliovirus and compared the same with neem oil [240]. The results revealed that NIM-76 inhibited the growth of various bacterial pathogens tested including *Escherichia coli* and *Kleibsiella pneumoniae.* The extract also showed antifungal activity against *Candida albicans* and antiviral activity against Poliovirus replication in Vero cell lines. Overall, NIM-76 showed stronger anti-microbial activity as compared to the neem oil. Neem seed kernel extract was found to be active against *Bacillus mycoides, B. thuringiensis, B. subtilis, Nocardia* sp., and *Corynebacterium fascians* in *in vitro* assays [241]. In another study, neem mouthwash was found to show antibacterial activity against salivary levels of *Streptococcus mutans* and *Lactobacillus* [242]. Neem leaf extract gel also showed antiplaque activity [243]. Polyester/cotton blend fabric treated with neem extract was reported to have antibacterial activity against both Gram-positive (*Bacillus subtilis*) and Gram-negative bacteria (*Proteus vulgaris*) [244]. Neem oil was also found to be active against *Staphylococcus aureus, Salmonella typhi, Pseudomonas aeruginosa,* and *Escherichia coli* [245, 246]. The tetranortriterpenoid, nimolicinol, isolated from neem, was reported to be moderately antibacterial against several human pathogenic bacteria [93, 95]. The antibacterial activity of neem leaf extract and various phytoconstituents of neem such as alkaloids, steroids, tannins, glycosides, flavonoids, and saponins were evaluated and confirmed to have antibacterial efficacies, with crude flavonoids revealing maximum antibacterial activities [247]. 9-Octadecanoic acid-hexadecanoic acid-tetrahydrofuran-3,4-diyl ester obtained from neem oil was found active against *Staphylococcus aureus, Escherichia coli,* and *Salmonella* sp. in *in vitro* assays [113]. M-Octadecanoic acid-3,4-tetrahydrofuran diester, isolated from the petroleum ether extract of neem oil, also showed potent antibacterial activity [248]. Alcoholic extracts of neem leaves were found to be active against the human bacterial pathogens *Bacillus pumillus, Pseudomonas aeruginosa*, and *Staphylococcus aureus* [249].

Antiviral activities

Foliar application of neem seed oil, when compared with neem seed oil-free extract, inhibited transmission of potato virus Y to sweet pepper by the green peach aphid, *Myzus persicae* (Sulzer) suggesting that the oil interferes with virus transmission [250]. A methanolic extract fraction of leaves of neem showed antiviral activity against the Coxsackie B group of viruses [251]. Crude aqueous extract of neem leaves was reported both *in vitro* and *in vivo* to display antiviral activity against the replication of Dengue virus type-2 [252]. Aqueous neem bark extract, at concentrations ranging from 50 to 100 µg/ml, when pre-incubated with herpes simplex virus type 1 (HSV-1), considerably blocked its entry into cells; additionally, virions treated with the extract failed to bind to the cells, suggesting role of the extract either as an attachment-blocker or having direct anti-HSV-1 property. Furthermore, cells treated with extract also inhibited herpes simplex virus type 1 glycoprotein-mediated cell-cell fusion and polykaryocytes formation, signifying an additional role of the bark extract at the viral fusion step [253]. The crude acidic extract of leaves and seeds and alkaline extract of seeds were found to show high antiviral activity against HSV-1 when compared with the well-known antiviral drug acyclovir [254].

Anticarcinogenic activities

Azadirone, a limonoidal constituent isolated from methanolic extract of neem flowers, was found to be a potent cytotoxic agent with good *in vitro* and *in vivo* activities [255]. The studies also revealed that the *α,β*-unsaturated enone moiety, or its equivalent conjugated system of A-ring, C-7 acetyloxy/chloroacetyloxy or keto group of B-ring and the furan moiety, are the structural requirements for the potent activity of azadirone and its analogs [255]. Four prenylated flavanones, 5,7,4′-trihydroxy-8-prenylflavanone, 5,4′-dihydroxy-7-methoxy-8-prenylflavanone, 5,7,4′-trihydroxy-3′,8-diprenylflavanone, and 5,7,4′-trihydroxy-3′,5′-diprenylflavanone, were isolated by activity-guided fractionation from the methanolic extract of the flowers of neem, which acted as potent antimutagens against Trp-P-1 (3-amino-1,4-dimethyl-5H-pyrido[4,3-b]indole) in the *Salmonella typhimurium* TA98 assay [61]. Aqueous extract of neem was found to show chemopreventive potential when given to Syrian male hamsters having 7,12-dimethylbenz[a]anthracene (DMBA) induced buccal pouch carcinogenesis by modulation of lipid peroxidation, antioxidants, and detoxification systems [256]. Pre-treatment with ethanolic neem leaf extract significantly lowered the concentration of lipid peroxides and increased antioxidant levels on induced oxidative stress by the potent gastric carcinogen N-methyl-N′-nitro-N-nitrosoguanidine (MNNG) in male Wistar rats suggesting its chemoprotective effects [257]. Significant anticarcinogenic potential was also found in leaf extracts of *A. indica* in a tumor model system ($p < 0.005$ to $p < 0.001$) [258]. Subapriya et al. (2005) suggested that the chemopreventive effects of ethanolic neem leaf extract might be mediated by the induction of apoptosis [259]. Treatment of rats by aqueous neem extracts significantly decreased the proliferating cell nuclear antigen labeling indices of colon epithelium and aberrant crypt foci, suggesting a chemopreventive role in the short-term colon carcinogenesis bioassay [260]. Nimbolide, a triterpenoid extracted from the flowers of the neem, was found to have antiproliferative activity and apoptosis-inducing property against U937, HL-60, THP1, and B16 cancer cell lines [261]. The acidic extract of leaves and neutral extract of seeds possessed anticancer activity, inhibiting *Ehrlich ascites* carcinoma cell line growth and IC_{50} values were 669.43 and 724.63 µg/ml, respectively [254]. 7-Deacetyl-7-benzoylepoxyazadiradione, 7-deacetyl-7-benzoylgeduin, and 28-deoxonimbolide exhibited potent cytotoxic activity against HL60 leukemia cells while 4 other compounds (7-benzoylnimbocinol, epoxyazadiradione, gedunin, and ohchinin acetate) exhibited cytotoxic activity against 1 or more cell lines [114]. Cytotoxic activities of nimbolide isolated from branches and leaves against HL-60 have also been reported [121]. Sulfonoquinovosyldiacylglyceride, a water-soluble constituent of dried neem leaves, showed anti-cancerous activity in human leukemic cell lines U937 and K562 with IC_{50} of 9 µg/ml [49]. Nimbolide was shown to exert apoptotic activity in estrogen-dependent (MCF-7) and estrogen-independent (MDA-MB-231) human breast cancer cell lines activating caspase-8, caspase-9, caspase-3, and cleavage of PARP [122]. Induction of apoptosis in human breast cancer cells by nimbolide ratifies its future in cancer treatment as a chemotherapeutic agent [122]. NIM-76, a volatile fraction of neem oil, was reported to have no mutagenic effects and regarded as safe concerning genotoxic potential in humans [262]. *In vitro* inhibition of growth of mouse sarcoma was found on treatment with neem leaf glycoprotein (25 µg/mice/wk subcutaneously for 4 wks) [263]. This anti-tumor immunity inhibiting the growth of mouse sarcoma was reported to be associated with increased expression of CD69, CD44, and Ki67 on CD8+ T cells [263]. Neem leaf glycoprotein showed no toxicity to various physiological functions of Swiss mice and Sprague-Dawley rats even though type 1 cytokines increased in serum with a decrease in type 2 cytokines and total IgG content in leaf glycoprotein-treated mice [264]. Change in type 1 cytokines were associated with increased anti-tumor immunity [264]. Neem oil limonoids were found to induce caspase-dependent and apoptosis-inducing factor-mediated apoptosis, as well as autophagy in cancer cells [265].

Hepatoprotective activities

Aqueous leaf extracts of neem significantly prevented changes in the serum levels of bilirubin, protein, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase, and prevented the histological changes, thus having an antihepatotoxic activity against the damage induced by antitubercular drugs in rats [266]. Chattopadhyay and Bandyopadhyay (2005) discussed the possible mechanism of hepatoprotective activity of neem leaf extracts against paracetamol-induced hepatic damage in rats and concluded that hepatoprotective activity was possibly due to its potent antioxidant activity [267]. Mercury-induced oxidative damage in hepatic tissues was improved with neem leaf extract through its antioxidant effects [268].

Antioxidant activities

Sithisarn et al. (2006) compared free radical scavenging activity of Siamese neem tree leaf extracts against the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical and reported that most active extract was obtained with the leaf decoction method showing antioxidant activity with half-maximal effective concentration (EC_{50}) of 31.4 µg/ml [269]. In another study, significant antioxidant properties were observed in leaf and bark extracts/fractions of neem, while bark was found to possess higher phenolic content than the leaves [270].

Effects on CNS

Anxiolytic activity of leaf extracts of *A. indica* was studied in rats [271]. Neem extracts could attenuate anxiogenic and appetite-suppressant effects of stress by decreasing the brain's 5-hydroxytryptamine and 5-hydroxyindolacetic acid concentration in albino Wistar rats [272]. The pharmacotherapeutic value of neem leaves was also seen in anxiety disorders of albino Wistar rats [273].

Molluscicidal activities

Singh and co-workers (1996) showed the effect of leaf, bark, cake, neem oil, and the neem-based pesticides, achook and nimbecidine of neem, against the snails *Lymnaea acuminata* and *Indopla-*

norbis exustus and found that pure azadirachtin was more toxic compared to synthetic molluscicides [274]. In another study, crude extracts of bark, roots, and leaves of neem at 500 mg/kg and 700 mg/kg were found lethal to edible tropical land snails *Archachatina marginata* and *Limicolaria aurora* (Jay) after exposure for 72 h and 48 h, respectively [275].

Insecticidal activities

The neem tree is well known for its insecticidal properties, which has been documented in a large assortment of studies. Insect growth-regulating properties were found in 23-O-methylnimocinolide and 1, 7-O-deacetyl-23-O-methyl-7*α*-O-senecioylnimocinolide [39] belonging to γ-hydroxybutenolides group of compounds. Siddiqui et al. (2002) reported desfurano-6-*α*-hydroxyazadiradione and 22, 23-dihydronimocinol as having insecticidal activity against the fourth instar larvae of mosquito (*Anopheles stephensi*) [36]. Two nitrogen-containing limonoids, salannolactam-21 and salannolactam-23, have been reported from neem seed kernels, which possess antifeedant activities [151]. Various tetranortriterpenoids–meliatetraolenone, zafaral, 6a-O-acetyl-7-deacetylnimocinol, meliacinol, 17-β-hydroxyazadiradione, azadironic acid, limocin-A, limocin-B, epoxyazadiradione, mahmoodin, gedunin, 7-decacetylgedunin, 1, 3-di-O-acetylvilasinin, 1-O-tigloyl-3-O-acetylvilasinin, nimbin, azadiradione, and 7-deacetylazadirone–isolated from different tissues of neem have been reported to either have insecticidal activities or insect anti-feeding activities (see ▶ **Table 1**). Additionally, azadirachtin and related compounds, such as 6-deactylnimbin, nimbolin B, salannin, 3-deacetylsalannin, salannol, and salannol acetate, have been isolated from various tissues of neem and also have insecticidal or insect anti-feeding properties. Insect growth-regulating activity was observed in desfuranoazadiradione, an octanortriterpenoid isolated from fresh fruit coats [77, 82]. Meliacinin, a dinortriterpenoid isolated from fruit coats, was found to be toxic against mosquito (*Anopheles stephensi*) [77, 78]. *β*-sitosterol, a steroid, has also shown insecticidal potential [276, 277]. Odoratone (protolimonoid), isolated from methanolic extract of fresh leaves, has demonstrated a lethal effect on the fourth instar larvae of mosquitoes (*A. stephensi*) [56]. Larvicidal properties of neem oil were also reported against *A. stephensi, Culex quinquefasciatus,* and *Aedes aegypti* [278].

Neem-based shampoos, amended with neem seed extract, are effective against all stages of head lice [279]. Extracts of neem oil [280], petroleum ether extracts of neem oil, and its 4 fractions separated by column chromatography [281] were reported to be lethal in *in vitro* assays against rabbit mite *Sarcoptes scabiei* var. *cuniculi* larvae. Further, octadecanoic acid-tetrahydrofuran-3,4-diyl ester isolated from an active fraction of the chloroform extract of neem oil was reported to have acaricidal *in vitro* activity against *S. scabiei* larvae [282]. Neem oil microemulsion was very effective against *Sarcoptes scabie* var. *cuniculi* larvae *in vitro* [283].

Antifilarial activities

Alcohol and aqueous extracts of flowers of *A. indica* showed inhibition of cattle filarial parasite *Setaria cervi* [284].

Synthesis and biological sources of azadirachtin

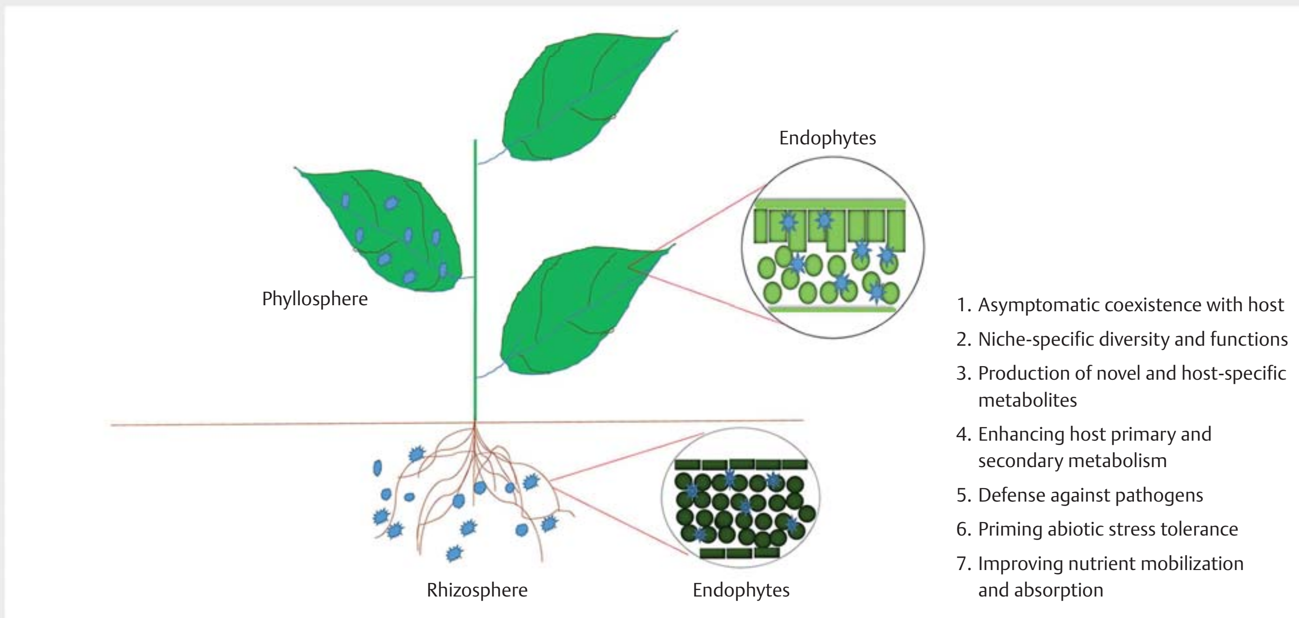
In addition to its remarkable insecticidal activity, azadirachtin also exhibits a range of other biological properties. The first complete structure of azadirachtin was elucidated by Nakanishi and coworkers in 1975 [285] using extensive NMR spectroscopy, which was further revised by Kraus in 1985 [87], who proposed a C13–C14 epoxide. However, it took 22 y for azadirachtin to be produced by total synthesis [286, 287]. Initially, Veitch and co-workers discussed the probable route leading to the successful synthesis of azadirachtin [288]. This was followed by Jauch (2008) [286] and Ley et al. (2008) [287] who reported the full mechanism of complete chemical synthesis of azadirachtin. Meanwhile, another group focused on the biotechnological approaches for the production of azadirachtin; its production was reported using *A. indica* cell suspension cultures [289]. Further, azadirachtin biosynthesis could be induced in hairy root cultures of *A. Indica* [290], which was enhanced in hairy root cultures of *A. indica* by Satdive et al. in 2007 [291]. Production of azadirachtin in neem callus and suspension cultures has also been reported [292]. Another method of androgenic culture of *A. indica* showed increased azadirachtin production [293]. In 2012, Kusari and coworkers reported the biosynthesis of azadirachtin by an endophytic fungus, *Eupenicillium parvum*, isolated from neem [294].

Endophytic microorganisms (endophytes)

Endophytes are one of the predominant classes of microorganisms, which reside inside healthy tissues of host plants; endophytes include bacteria, fungi, nematodes, and viruses. Fungal endophytes (or endophytic fungi) are a dynamic and multitrophic group of microorganisms that are ubiquitous in plants thriving in every ecological niche (▶ **Fig. 3**). Fungal endophytes have been found associated with algae [295], lichens [296], mosses [297], ferns [298], conifers [299], large trees [300], small trees [301], palms [302, 303], mangroves [304], halophytes [305], grasses [306], marine sponges [307], and seagrasses [308] to name a few. Endophytic fungi were isolated from every plant tissue including bark, flower, leaves, petioles, root, seed, and twigs [7, 309–311]. Further, endophytic fungi are well-established producers of a plethora of bioactive compounds and extracellular enzymes such as amylase, cellulase, chitinase, chitosonase, laccase, lipase, pectinase, and protease [312–315]. Being colonizers of host tissues, the endobiome plays a crucial role in creating an extra layer of protection to their host during several adverse conditions [316, 317, 373]. They also modulate host metabolism for enhanced production of high-value secondary metabolites in medicinal plants like *Withania, Coleus, Papaver*; this positive modulation is a result of significant-high expression of genes and transcription factors of biosynthetic pathways [318–320]. Occasionally, few endophytic species mimic host metabolic pathways and produce host signature metabolites independently [294]. Therefore, unmatched beneficial traits of the endophytes were well recognized by research communities, and several of these endophytes have been utilized for several industrial and agricultural purposes.

Fungal endophytic diversity of *A. indica*

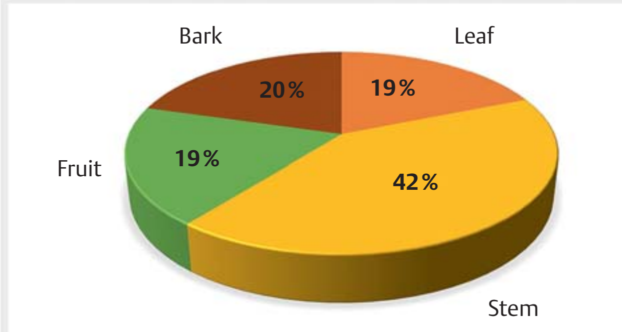
Following-up the cues on ethnobotanical history of neem, Rajagopal and Suryanarayanan (2000) investigated and isolated



▶ **Fig. 3** General representation of coexistence of and interaction between neem plants and associated endophytic microorganisms.

endophytic fungi from green and senescent leaves of *A. indica* from Chennai, India, continuously for 2 y on a monthly basis. They reported 5 selected endophytes, 4 of which were sterile forms and the fifth was identified as *Fusarium avenaceum* [321]. They proposed that the restricted number of endophytic fungal genera and the absence of common endophytic fungi in the neem leaves could be due to the antifungal metabolites present in the leaves. The frequency of colonization of green leaves by endophytes was maximal during the rainy season although no new endophyte species could be discovered. It was found that the occurrence of foliar endophytes was influenced by seasonal changes [311, 322]. Since this was also found to be the case with the foliar endophytes of neem, it was suggested that the occurrence of foliar endophytes in tropical trees was influenced by the environment, soil type, and chemistry of the host tissue [321]. Mahesh and co-workers (2005) studied endophytic mycoflora harboring the inner bark of *A. indica* and reported 77 endophytic fungal isolates belonging to 15 genera [323]. Among them, 71.4% were hyphomycetes, followed by 18.2% coelomycetes, 6.5% ascomycetes, and 3.9% sterile mycelia. The colonization frequency was found to be 38.5%. Although Rajagopal and Suryanarayanan (2000) recovered only *Fusarium avenaceum* and 4 sterile forms of endophytes [321], Mahesh and co-workers (2005) were able to recover endophytic genera such as *Curvularia, Cochlonema, Gliomastix*, and *Verticillium* sp. [323]. Later, the same group identified endophyte diversity in bark segments of *A. indica,* which exposed high species richness with an average of 20 species, and prevalent colonization of *Trichoderma* and *Chaetomium globosum* was observed [324]. Verma and co-workers (2007) studied the fungal endophytes of *A. indica* in several of its natural habitats in India and recovered a total of 233 isolates of endophytic fungi, representing 18 fungal taxa from segments of bark, stem, and leaves [310]. Interestingly, in the whole study, the authors observed that hyphomycetes were the most prevalent group (62.2%), followed by the coelomycetes (27.4%) and a minor percentage by mycelia-sterilia (7.7%). The leaf samples from all locations were nearly constant in their endophytic composition, whereas the bark samples showed maximum diversity at different locations. This study also revealed, for the first time, that endophytes of genera *Periconia, Stenella*, and *Drechslera* were associated with *A. indica*. Not only was the endophytic fungal colonization frequency higher in leaves (45.5%) than bark (31.5%), but the maximum species richness and frequency of colonization also were as well [310]. Shao and coworkers (2008) have studied the distribution of endophytic fungi in *A. Indica* from Yuanjiang county of Yunnan Province, PR China [325]. They isolated a total of 372 endophytic fungal strains from the stem, leaves, and fruits. *Colletotrichum* was found to be the most dominant genera, followed by *Alternaria* and *Xylaria.* Another group characterized 85 endophytic fungi belonging to 10 genera, which were isolated from 200 segments of fresh *A. indica* leaves collected from the Panchmarhi biosphere reserve [326]. Here, the most dominant endophytes observed were *Trichoderma, Pestalotiopsis*, and *Penicillium* sp.

Rajagopal and Suryanarayanan (2000) found that even though the endophytic genera *Phomopsis, Phyllosticta,* and *Xylaria* are ubiquitous and commonly isolated from many hosts, these were absent from the leaves of the neem plants under their study [321]. However, these genera were found to be endophytic in neem leaves by other studies [310, 323, 325]. Dominant endophytes fungi isolated from the inner bark of *A. indica* from South India were *Trichoderma, Penicillium,* and *Pestalotiopsis* spp. [323], while those from North India were typically *Phomopsis oblonga, Cladosporium cladosporioides, Pestalotiopsis* sp., *Trichoderma* sp., and *Aspergillus* sp. [310]. Further, isolated species had exhibited inhibitory properties against *Trichophyton, Microsporum* [327]. In China, *Colletotrichum* was reported as the most dominant genus, followed by *Alternaria* and *Xylaria* [325]. This clearly indicates that endophyte diversity and species richness are not only dependent on specific hosts but also are location and niche specific. This further illustrates the importance of sampling different tissues of a given plant at several locations to obtain an enormous species diversity of endophytes. Taken together, endophytic fungal diversity in neem has been found to be highest in stems (42%), followed by bark (20%), while leaves and fruits harbor a similar percentage of endophytic fungi (19%) (▶ **Fig. 4**). With the isolation of endophytic fungi from roots and fruits of neem, in addition to previous isolation and characterization from leaves, stems and bark, Verma and colleagues completed sampling of all organs of selected neem trees for their endophytic microflora [7, 300, 303]. Overall, a unique diversity pattern emerges from these studies: endophytic fungi isolated from *A. indica* belong mostly to the hyphomycetes, followed by coelomycetes and finally, ascomycetes [310, 313, 321, 323, 325].



▶ **Fig. 4** Percentage of the endophytic fungi isolated from different parts of neem.

Endophytic actinomycetes of *A. indica*

In addition to endophytic fungi, neem plants have been studied for the presence of associated endophytic actinomycetes. Kharwar and coworkers characterized 55 endophytic actinomycetes from 20 different samples, 60% of which showed *in vitro* inhibitory activity against 1 or more pathogenic fungi or bacteria [313]. Actinomycetes were most commonly recovered from roots (54.5% of all isolates), followed by stems (23.6%), and finally, leaves (21.8%). The dominant genus was *Streptomyces* (49.09% of all isolates), while *Streptosporangium* (14.5%), *Microbispora* (10.9%), *Streptoverticillium* (5.5%), *Sacchromonospora* sp. (5.5%), and *Nocardia* (3.6%) were also isolated. In another study, Gohain and coworkers identified the actinomycetes diversity of 6 medicinal plants collected from Gibbon wildlife sanctuary, Assam, and revealed that *A. indica* possesses the high Shannon diversity index (1.49) with predominance of *Streptomyces* species and *Streptomyces* significantly expressed Polyketide synthase-II (PKS) gene [328]. Endophytic actinomycetes species isolated from *A. indica* improved plant growth of tomato through the production of siderophores and Indole acetic acid, and inhibited the growth of the pathogen *Alternaria alternata* that causes blight disease in tomato [324]. Further, an actinomycete *Micromonospora costi* has been isolated from *A. indica* from Thailand. The unique characteristics of this species include the presence of meso-diaminopimelic acid in peptidoglycan and the presence of phospholipids like diphosphatidylglycerol, phosphatidylethanolamine, and phosphatidylinositol in the plasma membrane [329].

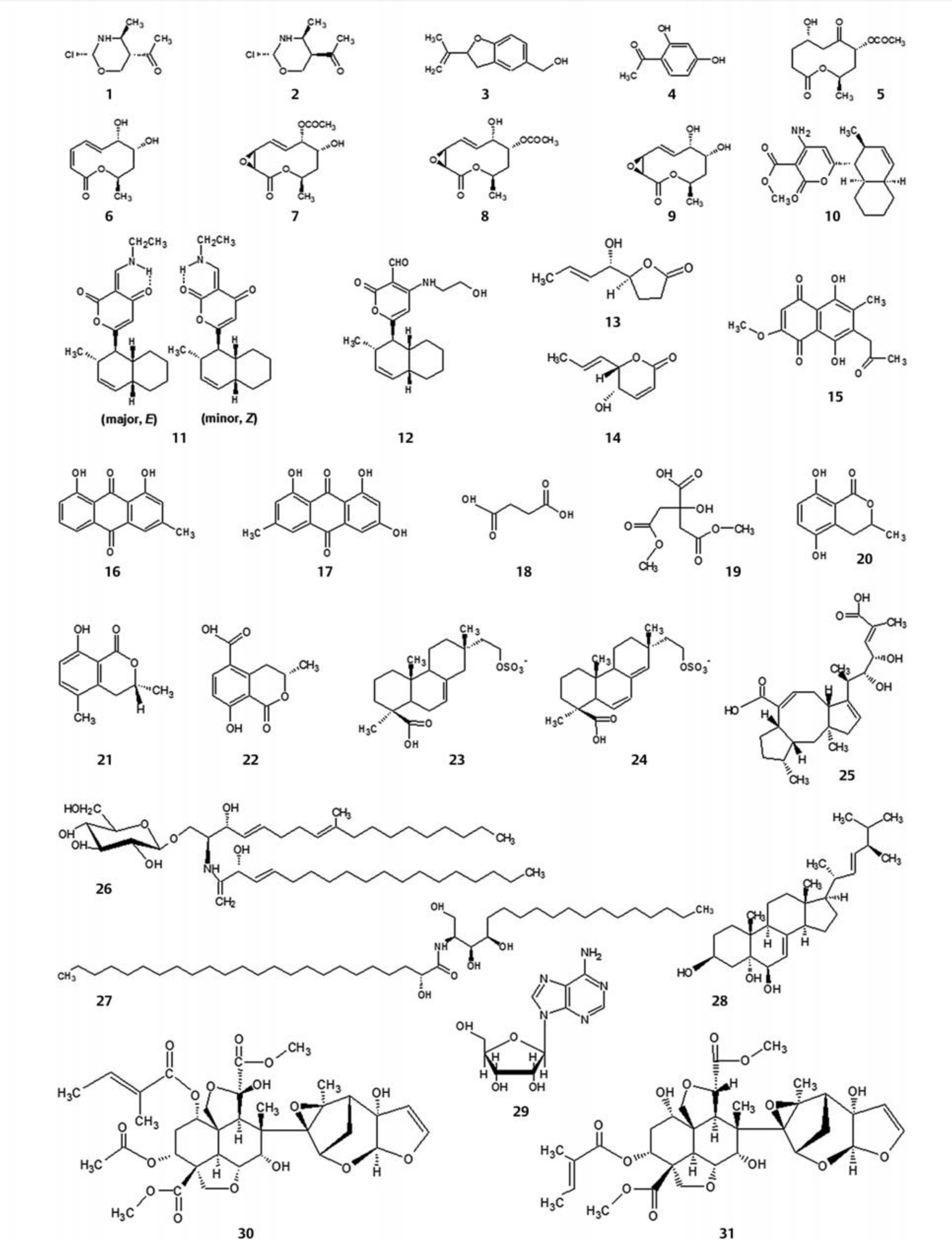
Metabolomics of Endophytes

In 1993, the landmark discovery of biosynthesis of the anticancer compound paclitaxel (Taxol) by endophytic *Taxomyces andreanae* [330] captured the attention of the scientific community towards endophytes as a treasure trove of novel, unique, bioactive natural products. A considerable number of discoveries followed the remarkable work, which cemented the virtually inexhaustible biosynthetic capabilities of endophytic fungi. Some important compounds produced by endophytic fungi are antifungal compounds such as cryptocandin A [331], cryptocin [332], ambuic acid [333, 334], pestaloside [335] and jesterone [336]; antibacterial compounds such as cytosporone A [337, 338] and javanicin [314]; anticancer compounds such as torreyanic acid [339], vincristine [340], chaetoglobosin A [341], penicillenols A1 and B1 [342], and camptothecin [343]; antioxidants like pestacin [344] and isopestacin [345]; and immunosuppressant subglutinols A and B [346] and HIV-1 integrase inhibitors [347]. Several reviews exemplify the vast chemical diversity of compounds produced by endophytes isolated from various plants prospected from different parts of the world [313, 348, 349]. Recently, Chutulo et al. (2018) briefly reported the metetabolites produced by endophytes isolated from neem plant and their activities [350]. The bioactive compounds produced by endophytes not only have an ecological significance but also provide a scientific handle to study the biochemical and molecular blueprints associated with their production [351]. Herein, we present detailed elaboration on the recent developments in compounds identified from the endophytic fungi of neem plant.

Bioactive natural compounds of endophytic fungi isolated from A. indica

Over 30 compounds have already been reported to be produced by neem-associated fungal endophytes. For instance, chlorinated oxazinane derivatives, 10-membered lactones, solanapyrone analogues, naphthaqinones, anthraquinones, napthodianthrone derivatives, and ring-C-seco-tetranortriterpenoids are some of the essential compound classes reported to be biosynthesized by endophytes associated with neem (▶ **Fig. 5** and **Table 2**).

Two new chlorinated, epimeric 1,3-oxazinane derivatives possessing nematicidal activity were characterized from *Geotrichum* sp. residing endophytically in leaves of neem [352], namely 1-ethanone (**1**) and 1-[(2R*,4S*,5R*)-2-chloro-4-methyl-1,3-oxazinan-5-yl]ethanone (**2**), an epimer of the first. Another nematicide active against the nematodes *Bursaphelenchus xylophilus* and *Panagrellus redivivus*, identified as [2,3-dihydro-2-(1-methylethenyl)-1-benzofuran-5-yl]methanol (**3**), was also reported from *Geotrichum* sp. in addition to 1-(2,4-dihydroxyphenyl)-ethanone (**4**) [352]. Ten-membered lactones viz. 8*α*-acetoxy-5*α*-hydroxy-7-oxodecan-9-olide (**5**), 7*α*,8*α*-dihydroxy-3,5-decadien-10-olide (**6**), 7*α*-acetoxymultiplolide A (**7**), 8*α*-acetoxymultiplolide A (**8**), and multiplolide A (**9**) have been reported from *Phomopsis* sp. isolated



▶ **Fig. 5** Bioactive natural compounds isolated from endophytic fungi of *A. indica*.

▶ **Table 2** Major bioactive compounds derived from endophytic fungi of *Azadirachta indica*.

Sl. No.	Compound	Derivative	Activity	Endophytic fungi	Reference
1	1-[(2R*,4S*,5S*)-2-chloro-4-methyl-1,3-oxazinan-5-yl]ethanone (**1**)	Chlorinated oxazinane derivate	Nematicidal	*Geotrichum* sp.	[352]
2	1-[(2R*,4S*,5R*)-2-chloro-4-methyl-1,3-oxazinan-5-yl]ethanone (**2**)	Chlorinated oxazinane derivate	Nematicidal	*Geotrichum* sp.	[352]
3	[2,3-dihydro-2-(1-methylethenyl)-1-benzofuran-5-yl]methanol (**3**)	Benzofuran derivative	n. a.	*Geotrichum* sp.	[352]
4	1-(2,4-dihydroxyphenyl)-ethanone (**4**)	Polyphenol	Nematicidal	*Geotrichum* sp.	[352]
5	8α-Acetoxy-5α-hydroxy-7-oxodecan-9-olide (**5**)	10-membered lactone ring	Antifungal	*Phomopsis* sp.	[353]
6	7α, α-Dihydroxy-3,5-decadien-10-olide (**6**)	10-membered lactone ring	Antifungal	*Phomopsis* sp.	[353]
7	7α-Acetoxymultiplolide A (**7**)	10-membered lactone ring	Antifungal	*Phomopsis* sp.	[353]
8	8α-Acetoxymultiplolide A (**8**)	10-membered lactone ring	Antifungal	*Phomopsis* sp.	[353]
9	Multiplolide A (**9**)	10-membered lactone ring	Antifungal	*Phomopsis* sp.	[353]
10	Solanapyrone N (Methyl 4-Amino-6-[(1R,2S,4aR,8aR)-1,2,4a,5,6,7,8,8a-octahydro-2-methylnaphthalen-1-yl]-2-oxo-2H-pyran-3-carboxylate) (**10**)	Solanapyrone analogues	Antifungal	*Nigrospora* sp.	[354]
11	Solanapyrone O (**11**)	Solanapyrone analogues	Antifungal	*Nigrospora* sp.	[354]
12	Solanapyrone C (**12**)	Solanapyrone analogues	Antifungal	*Nigrospora* sp.	[354]
13	Nigrosporalactone (**13**)	Lactones	Antifungal	*Nigrospora* sp.	[354]
14	Phomalactone (**14**)	Lactones	Antifungal	*Nigrospora* sp.	[354]
15	Javanicin (**15**)	Naphthaqinone	Antibacterial	*Chloridium* sp.	[314]
16	Chrysophanol (**16**)	Anthraquinone	Antibacterial	*Aspergillus aculeatus*	[355, 356]
17	Emodin (**17**)	Napthodianthrone derivative	Antibacterial, anticancerous	*Aspergillus aculeatus*	[355, 357, 358]
18	Succinic acid (**18**)	Dicarboxylic acid	Weak insecticidal activity against *Plutella xylostella*	*Aspergillus aculeatus* and *Xylaria* sp.	[355, 359]
19	1,5-Dimethyl citrate (**19**)	Oxobutanoate	n. a.	*Aspergillus aculeatus*	[352]
20	5-hydroxymellein (**20**)	Isocoumarin	Weak insecticidal activity against *Plutella xylostella*	*Xylaria* sp.	[359]
21	5-methylmellein (**21**)	Isocoumarin	Weak insecticidal activity against *Plutella xylostella*	*Xylaria* sp.	[359]
22	5-carboxymellein (**22**)	Isocoumarin	Weak insecticidal activity against *Plutella xylostella*	*Xylaria* sp.	[359]
23	Hymatoxin C (**23**)	Diterpene	Weak insecticidal activity against *Plutella xylostella*	*Xylaria* sp.	[359]
24	Hymatoxin D (**24**)	Diterpene	Weak insecticidal activity against *Plutella xylostella*	*Xylaria* sp.	[359]
25	Halorosellinic acid (**25**)	Ophiobolane sesterterpene	Weak insecticidal activity against *Plutella xylostella*	*Xylaria* sp.	[359]
26	Cerebroside C (**26**)	Sphingolipids	Weak insecticidal activity against *Plutella xylostella*	*Xylaria* sp.	[359]
27	(2S,3S,4R,2′R)-2-(2′-Hydroxytetracosa-noylamino)-octadecane-1,3,4-triol (**27**)	Ceramides (Lipids)	Weak insecticidal activity against *Plutella xylostella*	*Xylaria* sp.	[359]
28	Cerevisterol (**28**)	Steroids	Weak insecticidal activity against *Plutella xylostella*	*Xylaria* sp.	[359]
29	Adenosine (**29**)	Purine nucleoside	Weak insecticidal activity against *Plutella xylostella*	*Xylaria* sp.	[359]

continued

▶ **Table 2** *Continued*

Sl. No.	Compound	Derivative	Activity	Endophytic fungi	Reference
30	Azadirachtin A (**30**)	Ring-C-seco-tetrano-triterpenoids	Insecticidal activity	*Eupenicillium parvum*	[294]
31	Azadirachtin B (**31**)	Ring-C-seco-tetrano-triterpenoids	Insecticidal activity	*Eupenicillium parvum*	[294]

n. a.: not available

from stems of *A. indica*. These compounds exhibited antifungal activities against *Aspergillus niger, Botrytis cinerea, Fusarium avenaceum, Fusarium moniliforme, Helminthosporium maydis, Penicillium islandicum,* and *Ophiostoma minus* [353]. Multiplolide A (**9**), previously isolated from the fungus *Xylaria multiplex* [360], was also isolated from endophytic *Phomopsis* sp. associated with neem [353]. The main difference between multiplolide A (**9**) and 7*α*,8*a*-dihydroxy-3,5-decadien-10-olide (**6**) is that the epoxide moiety at C-3 and C-4 in the former is substituted by a double bond in the latter [360]. Solanapyrones have been previously reported as phytotoxins from *Ascochyta rabiei* [361–363] and *Alternaria solani* [364, 365]. Interestingly, 2 analogs solanapyrone N (**10**) and solanapyrone O (**11**) were isolated from *Nigrospora* sp. recovered from stems of *A. indica,* with both being structurally different in the substitution pattern of the *a*-pyrone unit compared to other solanapyrones [354]. Solanapyrone N (**10**), solanapyrone O (**11**), solanapyrone C (**12**), nigrosporalactone (**13**), and phomalactone (**14**) were shown to possess antifungal activities [354]. Structurally-related analogs of solanapyrones have also been isolated from an unidentified marine fungus associated with the surface of the green alga *Halimeda monile,* which demonstrated anti-algal activity [366]. Wu et al. [367] isolated guanine sesquiterpenes and isopimarane diterpenes from *Xylaria sp.* isolated from *A. indica,* and these compounds have shown inhibitory activities against *Candida albicans, Hormodendrum compactum*, and *Pyricularia oryzae with* MIC values ranging between 16 µg to 256 µg/ml. Similarly, 5 new guanine sesquiterpenes were further isolated from *Xylaria sp.* which also possesses antipathogenic activities [368]. Recently, Chatterjee et al. [369] identified the metabolites produced by *Alternaria alternata* isolated from *A. indica* showing inhibitory activities against Gram-negative and Gram-positive bacteria.

The highly functionalized antibacterial naphthaquinone, javanicin (**15**), has been reported from an endophytic fungus *Chloridium* sp. isolated from roots of *A. indica* [314], which displayed strong inhibition of *Pseudomonas aeruginosa* and *P. fluorescens*. Chrysophanol (**16**), emodin (**17**), succinic acid (**18**), and 1,5-dimethyl citrate (**19**) were obtained from the broth extract of an endophytic fungus *Aspergillus aculeatus*, a resident of *A. indica* [355]. Chrysophanol (1,8-dihydroxy-3-methylanthracenedione) (**16**), an anthraquinone responsible for antimicrobial efficacy against *Bacillus subtilis* and *Staphylococcus aureus*, was detected in the extract of *Colubrina greggii* [356]. Emodin (**17**) and related compounds were previously described as having significant inhibitory activities against P-388 leukemia in mice [357]. Emodin (**17**), postulated as the primary precursor in the endophytic biochemical pathway to the naphthodianthrone derivative hypericin, also showed antimicrobial activity against the Gram-positive bacterium *Staphylococcus aureus*, Gram-negative bacteria *Klebsiella pneumoniae* f. sp. *ozaenae, Pseudomonas aeruginosa, Salmonella enterica* f. sp. *enterica*, and *Escherichia coli*, and fungal organisms *Aspergillus niger* and *Candida albicans* [358]. Eleven compounds, namely 5-hydroxymellein (**20**), 5-methylmellein (**21**), 5-carboxymellein (**22**), hymatoxin C (**23**), hymatoxin D (**24**), halorosellinic acid (**25**), cerebroside C (**26**), (2S,3S,4R,2′R)-2-(2′-hydroxytetracosanoylamino)-octadecane-1,3,4-triol (**27**), cerevisterol (**28**), adenosine (**29**), and succinic acid (**18**) have been reported to be produced by endophytic *Xylaria* sp. YC-10 isolated from the stems of *A. indica* collected in Yuanjiang County, Yunnan Province, P. R. China [359]. Although all the compounds exhibited weak insecticidal activity against *Plutella xylostella*, 9 of these compounds were reported from *Xylaria* for the first time [359]. Further, Verma et al. [370] attempted to synthesize silver nanoparticles from the extracts of endophytic fungus *Aspergillus clavatus* and tested against human pathogens such as *Candida albicans, Pseudomonas fluorescens*, and *Escherichia coli*, and they were effective against pathogens at 9.7 µg/ml (minimum fungicidal concentration) and 5.83 µg/ml (minimum inhibitory concentration). Kusari et al. (2012) identified and quantified azadirachtin A (**30**) and B (**31**) as biosynthetic products of a novel neem-associated endophytic fungus, *Eupenicillium parvum* [294]. This study highlighted an interesting plant-endophyte association where plant “mimetic” compounds are produced by endophytes to render similar functional traits in their ecological habitats.

Outlook

A. indica (neem) and its endophytic microflora represent an extensive repertoire of diverse natural products having different biological activities. On the one hand, neem (host plant) is a rich source of compounds such as the azadirachtins and related tetranortriterpenoids. On the other hand, endophytes associated with neem have a massive potential in synthesizing bioactive and chemically novel compounds. It is noteworthy that a large number of diverse endophytic fungi and actinomycetes have been isolated from *A. indica* in a relatively small period. Concomitantly, a large number of compounds have been isolated from neem and its endophytes, even though their biochemistry and overall ecological connotations are not clearly understood. Except for a few studies, endophytic microorganisms of neem remain poorly investigated. Recently, an epigenetic study was conducted to induce the antimicrobial activity and production of cryptic metabolites from *Streptomyces coelicolor* (AZRA 37) of neem plant, and the increased antimicrobial activity coupled with induced protein production were registered [371]. Extensive research is required to assess the hidden endophytic populations of neem. In particular, endophytic actinomycetes associated with neem can serve as a precious and reliable resource of novel compounds, given that they are well-known prolific producers of bioactive metabolites [372]. It has already been firmly established that endophytes have unique functions in hosts such as plant protection, nutrient supply, phosphate solubilization, and mineral transport. Besides, endophytic fungi can also confer a profound impact on the host system by not only enhancing growth and fitness but also strengthening their tolerances to abiotic and biotic stresses. It has been proposed that during evolution, some co-existing endophytes and their host plants have established a unique relationship with one another and significantly influenced the formation of secondary metabolites in plants such as neem. These findings open new platforms for enhancing growth as well as for improved production of valuable metabolites using endophytes in the host plant. However, mechanisms underlying plant-endophyte interaction are still open to future research. It is known that during endophyte infection, selected plant-specific metabolites play a significant role in colonization and the establishment of endophytic interactions. These substances not only play a crucial role in defense and competition but also might be needed for specific interaction and communication with the endophyte(s). As highlighted in this review, endophytic associations have been studied, using a bird's-eye view from the host plant's side, which resulted in detailed and comprehensive knowledge related to various microbes associated with different species or cultivars. However, how the host plant (*A. indica*) responds varies depending on the endophyte strain and plant environment. The mechanisms behind such selective priming remains obscure. Extricating the changes in transcriptome and, subsequently, metabolome – both of neem as well as associated endophytes – under the influence of abiotic and biotic environmental factors will throw light into the genetic and biochemical mechanisms underlying neem-endophyte interactions.

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Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] National Research Council. Neem: A Tree for solving global Problems. Washington, DC: National Academy Press; 1992. doi:10.17226/1924

[2] Ludwig-Muller J. Plants and endophytes: equal partners in secondary metabolite production? Biotechnol Letters 2015; 37: 1325–1334

[3] Hawksworth DL. The fungal dimension of biodiversity: magnitude, significance, and conservation. Mycol Res 1991; 95: 641–655

[4] De Bary A. Morphologie und Physiologie der Pilze, Flechten, und Myxomyceten. In: Hofmeister W. Hofmeister's Handbook of Physiological Botany, vol 2. Leipzig: W. Engelmann; 1866

[5] Wilson D. Endophyte the evolution of a term, and clarification of its use and definition. Oikos 1995; 73: 274–276

[6] Mostert L, Crous PW, Petrini O. Endophytic fungi associated with shoots and leaves of *Vitis vinifera*, with specific reference to the *Phomopsis viticola* complex. Sydowia 2000; 52: 46–58

[7] Verma VC, Gond SK, Kumar A, Kharwar RN, Boulanger LA, Strobel GA. Endophytic fungal flora from roots and fruits of an Indian neem plant *Azadirachta indica* A. Juss., and impact of culture media on their isolation. Indian J Microbiol 2011; 51: 469–476

[8] Roxburgh W. Description of Indian Plants. New Delhi, India: Today and Tomorrows Printers and Publishers; 1874

[9] Ahmed S. Economic, Socio-Economic and Policy Considerations on Neem's current Use for Pest Management. In: Schmutterer H, ed. The Neem Tree *Azadirachta indica* A. Juss. and other Meliaceous Plants. Weinheim, Germany: VCH Verlagsgesellschaft; 1995: 559–578

[10] De Jussieu A. Memoire sur le group des Meliacees. Mem Mus Hist Nat 1830; 19: 153–304

[11] Dube R. Neem Kranti. Lucknow: Shubham Prakashan; 1996

[12] Siddiqui S. A note on the isolation of three new bitter principles from the neem oil. Curr Sci 1942; 11: 278–279

[13] Siddiqui S, Mitra C. Utilization of neem oil and its bitter constituents (nimbidin series) in the pharmaceutical industry. J Sci Ind Res 1945; 4: 5–10

[14] Islam M, Al-Amin M, Siddiqi MMA, Akter S, Haque MM, Sultana N, Chowdhury AMS. Isolation of quercetin-3-o-beta-d-glucopyranoside from the leaves of *Azadirachta Indica* and antimicrobial and cytotoxic screening of the crude extracts. Dhaka Univ J Sci 2012; 60: 11–14

[15] Siddiqui BS, Ali ST, Ali SK. Chemical Wealth of *Azadirachta indica* (Neem). In: Singh KK, Phogat S, Tomar A, Dhillon RS, eds. Neem. I. K. New Delhi: International Publishing House Pvt; 2009: 171–207

[16] Chen JJ, Chang YL, Teng CM, Chen IS. Anti-platelet aggregation alkaloids and lignans from *Hernandia nymphaeifolia*. Planta Med 2000; 66: 251–256

[17] Rasheed M. Studies on the chemical Constituents of *Azadirachta indica* A. Juss (Naeem) [PhD Dissertation]. Karachi: University of Karachi; 2002

[18] Mori M. (n-Hexacosanol and n-Octacosanol: feeding stimulants for larvae of the silkworm, *Bombyx mori*. J Insect Physiol 1982; 28: 969–973

[19] Schmutterer H, Ascher KRS. Natural Pesticides from the Neem Tree (*Azadirachta indica* A Juss) and other tropical Plants. In: Proceedings of the 2nd International Neem conference, Rauischholzhausen, Federal Republic of Germany. Eschborn, Germany: Deutsche Gesellschaft fur Technische Zusammenarbeit (GTZ) GmbH; 1983

[20] Awasthi YC, Mitra C. Constituents of *Melia indica* leaves. Phytochemistry 1971; 10: 2842

[21] Powell JW. Nuclear magnetic resonance spectroscopy. A correlation of the spectra of some meliacins and their derivatives. J Chem Soc C 1966; 1794–1798

[22] Kraus W, Cramer R. Neue Tetranortriterpenoide mit Insektenfrasshemmender Wirkung aus Neem Oil. Liebigs Ann Chem 1981: 181–189

[23] Nair SM, Gopal SD, Isaac D. Optimised isolation procedure for biologically active compounds nimbolide and 28-deoxonimbolide from *Azadirachta indica* leaves. Phytochemistry 1997; 46: 1177–1178

[24] Zhao G, Etherton TD, Martin KR, West SG, Gillies PJ, Kris-Etherton PM. Dietary alpha-linolenic acid reduces inflammatory and lipid cardiovascular risk factors in hypercholesterolemic men and women. J Nutr 2004; 134: 2991–2997

[25] Miller NJ, Sampson J, Candeias LP, Bramley PM, Rice-Evans CA. Antioxidant activities of carotenes and xanthophylls. FEBS Lett 1996; 384: 240–242

[26] Chakrabortty T, Verotta L, Poddar G. Evaluation of *Azadirachta indica* leaf extract for hypoglycaemic activity in rats. Phytother Res 1989; 3: 30–32

[27] Verma VS. Study on the effect of flavonoids on the infectivity of potato virus X. Zentralbl Bakteriol Parasitenkd Infektionskr Hyg 1973; 128: 467–472

[28] Shah W, Rane N, Kekare MB, Vaidya V. Estimation of two bioactive compounds from *Azadiracta indica* A. Juss. leaves using HPLC. Int J Pharma Bio Sci 2010; 1: 1–7

[29] Deschner EE, Ruperto J, Wong G, Newmark HL. Quercetin and rutin as inhibitors of azoxymethanol-induced colonic neoplasia. Carcinogenesis 1991; 12: 1193–1196

[30] Basak SP, Chakraborty DP. Chemical investigation of *Azadirachta indica* leaf (*Melia azadirachta*). J Indian Chem Soc 1968; 45: 466–467

[31] Siddiqui S, Mahmood T, Siddiqui BS, Faizi S. Studies on the norterpenoidal constituents of *Azadirachta indica*. Pak J Sci Ind Res 1985; 28: 1

[32] Basu NM, Ray GK, De MK. The vitamin-C and carotene content of several herbs and flowers used in Ayurvedic system of medicine. J Indian Chem Soc 1947; 24: 358–360

[33] Garg HS, Bhakuni DS. 2′,3′-Dehydrosalannol, a tetranortriterpenoid from *Azadirachta indica* leaves. Phytochemistry 1985; 24: 866–867

[34] Kraus W, Gutzeit H, Bokel M. 1,3-diacetyl-11,19-deoxo-11-oxomeliacarpin, a possible precursor of azadirachtin from *Azadirachta indica* A. Juss. (Meliceae). Tetrahedron Lett 1989; 30: 1797–1798

[35] Siddiqui S, Siddiqui BS, Fiazi S, Mahmood T. Isoazadirolide, a new tetranortriterpenoid from *Azadirachta indica* A. Juss (Meliaceae). Heterocycles 1986; 24: 3163–3167

[36] Siddiqui BS, Afshan F, Faizi S, Naqvi SNH, Tariq RM. Two new triterpenoids from *Azadirachta indica* and their insecticidal activity. J Nat Prod 2002; 65: 1216–1218

[37] Siddiqui S, Siddiqui BS, Mahmood T, Fiazi S. Tetranortriterpenoid from *Azadirachta indica* A. Juss (Meliaceae). Heterocycles 1989; 29: 87–96

[38] Siddiqui S, Faizi S, Mahmood T, Siddiqui BS. Isolation of a new tetranortriterpenoid from *Azadirachta indica* A. Juss (Meliaceae). Heterocycles 1986; 24: 1319–1324

[39] Siddiqui BS, Afshan F, Ghiasuddin, Faizi S, Naqvi SNH, Tariq RM. New insect-growth-regulator meliacin butenolides from the leaves of *Azadirachta indica* A. Juss. J Chem Soc Perkin Trans I 1999: 2367–2370

[40] Van der Nat JM, Hart LA, Van der Sluis WG, Van Dijk H, Van den Berg AJ, de Silva KT, Labadie RP. Characterization of anticomplement compounds from *Azadirachta indica*. J Ethnopharmacol 1989; 27: 15–24

[41] Pachapurkar RV, Kornule PM. Tetranortriterpenoids from the leaves of *Azadirachta indica*. Acta Ciencia Indica 1983; 9 C: 55–59

[42] Subapriya R, Nagini S. Medicinal properties of neem leaves: A review. Curr Med Chem Anticancer Agents 2005; 5: 149–156

[43] Pachapurkar RV, Kornule PM, Narayanan CR. A new hexacyclic tetranortriterpenoid. Chem Lett 1974; 4: 357–358

[44] Siddiqui S, Faizi S, Mahmood T, Siddiqui BS. Two new insect growth regulator meliacins from *Azadirachta indica* A. Juss (meliaceae). J Chem Soc Perkin Trans 1 1986: 1021–1025

[45] Siddiqui BS, Afshan F, Gulzar T, Hanif M. Tetracyclic triterpenoids from the leaves of *Azadirachta indica*. Phytochemistry 2004; 65: 2363–2367

[46] Afshan F. Studies on the chemical constituents of the leaves of *Azadirachta indica* (Naeem) [PhD Dissertation]. University of Karachi: Karachi; 2002

[47] Bruhn A, Bokel M, Kraus W. 4*α*-6*α*-Dihydroxy-A-homoazadiron, ein neues Tetranortriterpenoid aus *Azadirachta indica* A. Juss (meliaceae). Tetrahedron Lett 1984; 25: 3691–3692

[48] Ragasa YC, Nacpil ZD, Natividad GM, Tada M, Coll JC, Rideout JA. Tetranotriterpenoids from *Azadirachta indica*. Phytochemistry 1997; 46: 555–558

[49] Bharitkar YP, Bhattacharya S, Das T, Roy M, Besra SE, Gomes A, Mondal NB, Banerjee S. Anti-leukemic activity of sulfonoquinovosyldiacylglyceride (SQDG): a constituent of *Azadirachta indica* leaves. Med Chem Res 2013; 22: 22–27

[50] Podder G, Mahato SB. Azadirachtanin, a new limonoid from the leaves of *Azadirachta indica*. Heterocycles 1985; 23: 2321–2325

[51] Siddiqui S, Tariq M, Bina SS, Shaheem F. Isolation of a triterpenoid from *Azadirachta indica*. Phytochemistry 1986; 25: 2183–2186

[52] Siddiqui S, Faizi S, Siddiqui BS. Studies on the chemical constituents of *Azadirachta indica* A. Juss (Meliaceae) Part I: isolation and structure of a new tetranortriterpenoid – nimolicinol. Heterocycles 1984; 22: 295–298

[53] Govindachari TR, Malathi R, Gopalakrishnan Geetha, Suresh G, Rajan SS. Isolation of a new tetranortriterpenoid from the uncrushed green leaves of *Azadirachta indica*. Phytochemistry 1999; 52: 1117–1119

[54] Siddiqui BS, Afshan F, Faizi S. Three novel tetracyclic triterpenoids of biogenetic interest from the leaves of *Azadirachta indica*. Tetrahedron 2001; 57: 10281–10286

[55] Perez-Gutierrez RM, Damian-Guzman M. Meliacinolin: a potent *α*-glucosidase and *α*-amylase inhibitor isolated from *Azadirachta indica* leaves and *in vivo* antidiabetic property in streptozotocin-nicotinamide-induced type 2 diabetes in mice. Biol Pharm Bull 2012; 35: 1516–1524

[56] Siddiqui BS, Afshan F, Gulzar T, Sultana R, Naqvi SN, Tariq RM. Tetracyclic triterpenoids from the leaves of *Azadirachta indica* and their insecticidal activities. Chem Pharm Bull 2003; 51: 415–417

[57] Siddiqui BS, Afshan F, Ghiasuddin, Faizi S, Naqvi SN, Tariq RM. Two insecticidal tetranortriterpenoids from *Azadirachta indica*. Phytochemistry 2000; 53: 371–376

[58] Kraus W, Bokel M, Bruhn A, Cramer R, Klaiber I, Klenk A, Nagl G, Pohnl H, Sadlo H, Vogler B. Structure determination by NMR of azadirachtin and related compounds from *Azadirachta indica* A. Juss. (Meliaceae). Tetrahedron 1987; 43: 2817–2830

[59] Nanduri S, Banstola KP. Neeflone, a new tetranortriterpenoid from the flowers of *Azadirachta indica* A. Juss (Meliaceae). ChemInform 1996; 27: 1019–1020

[60] Siddiqui BS, Ali ST, Rasheed M, Kardar MN. Chemical constituents of the flowers of *Azadirachta indica*. Helv Chim Acta 2003; 86: 2787–2796

[61] Nakahara K, Roy MK, Ono H, Maeda I, Kameyama MO, Yoshida M, Trakoontivakorn G. Prenylated flavanones isolated from flowers of *Azadirachta indica* (the Neem Tree) as antimutagenic constituents against heterocyclic amines. J Agric Food Chem 2003; 51: 6456–6460

[62] Siddiqui BS, Tariq Ali S, Kashif Ali S. A new flavanoid from the flowers of *Azadirachta indica*. Nat Prod Res 2006; 20: 241–245

[63] Subramanian SS, Nair AGR. Melicitrin, a new myricetin glycoside from the flowers of *Melia azadirachta*. Indian J Chem 1972; 10 B: 452

[64] Siddiqui BS, Ali ST, Rajput MT, Gulzar T, Rasheed M, Mehmood R. GC-based analysis of insecticidal constituents of the flowers of *Azadirachta indica* A. Juss. Nat Prod Res 2009; 23: 271–283

[65] Lavie D, Jain MK, Kirson I. Terpenoids. Part VI. The complete structure of melianone. J Chem Soc 1967: 1347–1351

[66] Su RH, Kim M, Yamamoto T, Takahashi S. Antifeeding constituents of *Phellodendron chinense* fruit against *Reticulitermes speratus*. J Pesticide Sci 1990; 15: 567–572

[67] Siddiqui S, Siddiqui BS, Faizi S, Tariq M. Studies on the chemical constituents of *Azadirachta indica.* A. Juss (Meliaceae) Part-VI. J Chem Soc 1986; 8: 341–347

[68] Koul O, Multani JS, Goomber S, Daniewski WM, Berlozecki S. Activity of some nonazadirachtin limonoids from *Azadirachta indica* against lepidopteran larvae. Australian J Entomol 2004; 43: 189–195

[69] Siddiqui S, Siddiqui BS, Faizi S. Studies in the chemical constituents of *Azadirachta indica* Part II: isolation and structure of the new triterpenoid azadirachtol. Planta Med 1985; 51: 478–480

[70] Malathi R, Rajan SS, Gopalakrishnan G, Suresh G. Azadirachtol, a tetranortriterpenoid from neem kernels. Acta Crystallogr C 2002; 58: 708–710

[71] Siddiqui S, Faizi S, Siddiqui BS, Ghiasuddin. Constituents of *Azadirachta indica*: isolation and structure elucidation of a new antibacterial tetranortriterpenoid, mahmoodin, and a new protolimonoid, naheedin. J Nat Prod 1992; 55: 303–310

[72] Siddiqui S, Siddiqui BS, Ghiasuddin, Faizi S. Tetracyclic triterpenoids of the fruit coats of *Azadirachta indica*. J Nat Prod 1991; 54: 408–415

[73] Kraus W, Cramer R. 17-epi-Azadiradion und 17-*β*-hydroxy-Azadiradion, zwei neue Inhaltsstoffe aus *Azadirachta indica* A. Juss. Tetrahedron Lett 1978; 27: 2395–2398

[74] Nathan SS, Kalaivani K, Murugan K. Effects of neem limonoids on the malaria vector *Anopheles stephensi* Liston (Diptera: Culicidae). Acta Trop 2005; 96: 47–55

[75] Kraus W, Bokel M. Neue Tetranortriterpenoide aus *Melia azedarach* Linn. (Meliaceae). Chem Ber 1981; 114: 267–275

[76] Rojatkar SR, Sawaikar DD, Nagasampagi BA. New tetra and Pentanortriterpenoids from *Azadirachta indica*. India: World Neem Conference; 1993: 203

[77] Siddiqui BS, Rasheed M, Ghiasuddin, Faizi S, Naqvi SNH, Tariq RM. Biologically active triterpenoids of biogenetic interest from the fresh fruit coats of *Azadirachta indica*. Tetrahedron 2000; 56: 3547–3551

[78] Tariq RM, Naqvi SNH, Rasheed M, Siddiqui BS, Gabol K, Zafar SMN. Enzyme inhibition by neem fruit *coat extract*, two fractions and four pure compounds in treated 4th instar larvae of *Anopheles stephensi* Liston (O. T. Wild-strain). Pak J Entomol 2009; 24: 9–14

[79] Siddiqui S, Siddiqui BS, Ghiasuddin, Faizi S. Terpenoids from fruit coatings of *Azadirachta indica*. Phytochemistry 1991; 30: 1615–1619

[80] Siddiquin BS, Rasheed M. Three new triterpenoids from *Azadirachta indica*. Helvetica Chimica Acta 2001; 84: 1962–1968

[81] Siddiqui S, Mahmood T, Faizi S, Siddiqui BS. Studies in the chemical constituents of *Azadirachta indica* A. Juss (Meliaceae): Part 10. Isolation and structure elucidation of isonimolicinolide, the first 17-acetoxytetranortriterpenoid and nimolicinoic acid, the first hexanortriterpenoid with an apoeuphane (apotirucallane) Skeleton. J Chem Soc Perkin Trans I 1987: 1429–1432

[82] Siddiqui BS, Ghiasuddin, Faizi S, Siddiqui S. Triterpenoids from the fresh fruit coats of *Azadirachta indica*. Phytochemistry 1992; 31: 4275–4278

[83] Siddiqui BS, Rasheed M, Ilyas F, Gulzar T, Tariq RM, Naqvi SN. Analysis of insecticidal *Azadirachta indica* A. Juss. fractions. Z Naturforsch C 2004; 59: 104–112

[84] Siddiqui BS, Ghiasuddin, Faizi S. Tetracyclic triterpenoids of the fruit coats of *Azadirachta indica*. Phytochemistry 1998; 47: 1631–1636

[85] Lee JY, Lee JY, Yun BS, Hwang BK. Antifungal activity of *β*-asarone from rhizomes of *Acorus gramineus*. J Agric Food Chem 2004; 52: 776–780

[86] Siddiqui BS, Ghiasuddin G, Faizi S, Rasheed M. Triterpenoids of the fruit coats of *Azadirachta indica*. J Nat Prod 1999; 62: 1006–1009

[87] Kraus W, Bokel M, Klenk A, Pöhn H. The structure of azadirachtin and 22,23-dihydro-23*β*-methoxyazadirachtin. Tetrahedron Lett 1985; 26: 6435–6438

[88] Luo XD, Wu SH, Ma YB, Wu DG. Four triterpenoids from neem extracts and their insecticidal activities. Nat Prod Res Dev 2001; 13: 9–13

[89] Sankaram AVB, Murthy MM, Bhaskaraiah K, Subramany AM, Sultana N, Sharma HC, Leuschner K, Ramaprasad G, Sitaramaiah S, Rukmini C, Rao PU. Chemistry, biological Activity and Utilization Aspects of some promising Neem Extractives. In: Schmutterer H, Ascher KRS, eds. Natural Pesticides from the Neem Tree and other tropical Plants. Eschborn, Germany: German Society for Technical Cooperation (GTZ); 1986: 127–148

[90] Thakur RS, Singh SD, Goswami A. Biological and medicinal applications of *Azadirachta indica* A. Juss. Curr Res Med Aromat Plants 1981; 3: 135–140

[91] Kraus W, Cramer R, Sawitzki G. Tetranortriterpenoids from the seeds of *Azadirachta indica*. Phytochemistry 1981; 20: 117–120

[92] Alam A, Haldar S, Thulasiram HV, Kumar R, Goyal M, Iqbal MS, Pal C, Dey S, Bindu S, Sarkar S, Pal U, Maiti NC, Bandyopadhyay U. Novel anti-inflammatory activity of epoxyazadiradione against macrophage migration inhibitory factor: inhibition of tautomerase and pro-inflammatory activities of macrophage migration inhibitory factor. J Biol Chem 2012; 287: 24844–24861

[93] Akihisa T, Noto T, Takahashi A, Fujita Y, Banno N, Tokuda H, Koike K, Suzuki T, Yasukawa K, Kimura Y. Melanogenesis inhibitory, anti-inflammatory, and chemopreventive effects of limonoids from the seeds of *Azadirachta indicia* A. Juss. (neem). J Oleo Sci 2009; 8: 581–594

[94] Hallur G, Sivramakrishnan A, Bhat SV. Three new tetranortriterpenoids from neem seed oil. J Nat Prod 2002; 65: 1177–1179

[95] Narayanan CR, Pachapurkar RV, Sawant BM, Wadia MS. Vepinin, a new constituent of neem oil. Indian J Chem 1969; 7: 187

[96] Saxena N, Kumar Y. Chemistry of Azadirachtin and other bioactive Isoprenoids from Neem (*Azadiricta indica* A. Juss.). In: Singh KK, Phogat S, Tomar A, Dhillon RS, eds. Neem. I. K. New Delhi: International Publishing Pvt; 2009: 208–230

[97] Kraus W, Bokel M, Schwinger M, Vogler B, Soellner R, Wendisch D, Steffens R, Wachendorff U. The Chemistry of Azadirachtin and other insecticidal Constituents of Meliaceae. In: Van Beek T, Breteler H, eds. Phytochemistry and Agriculture. New York: Oxford University Press; 1993: 18–39

[98] Pant N, Garg HS, Madhusudanan KP, Bhakuni DS. Sulfurous compounds from *Azadirachta indicia* leaves. Fitoterapia 1986; 57: 302

[99] Balandrin MF, Lee SM, Klocke JA. Biologically active volatile organosulfur compounds from seeds of the neem tree, *Azadirachta indica* (Meliaceae). J Agric Food Chem 1988; 36: 1048–1054

[100] Lavie D, Levy EC, Jain MK. Limonoids of biogenetic interest from *Melia azadirachta*. Tetrahedron 1971; 27: 3927–3939

[101] Uddin SJ, Nahar L, Shilpi JA, Shoeb M, Borkowski T, Gibbons S, Middleton M, Byres M, Sarker SD. Gedunin, a limonoid from *Xylocarpus granatum*, inhibits the growth of CaCo-2 colon cancer cell line *in vitro*. Phytother Res 2007; 21: 757–761

[102] Gaikwad BR, Mayelvaganan T, Vyas BA, Bhat SV. Nimbocinol and 17-epinimbocinol from the nimbidin fraction of neem oil. Phytochemistry 1990; 29: 3963–3965

[103] Henderson R, McCrindle R, Melera A, Overton KH. Tetranortriterpenoids. IX. The constitution and stereochemistry of salanin. Tetrahedron 1968; 24: 1525–1528

[104] Kubo I, Matsumoto T, Klocke JA. New ecdysis inhibitory limonoid deacetylazadirachtinol isolated from *Azadirachta indica* (Meliaceae) oil. Tetrahedron 1986; 42: 489–496

[105] Yamasaki BR, Ritland TG, Bornby MA, Klocke JA. Isolation and purification of salanin from neem seeds and its quantitation in neem and chinaberry seeds and leaves. J Chromatography 1988; 447: 277–283

[106] Mitchell MJ, Smith SL, Johnson S, Morgan ED. Effects of the neem tree compounds azadirachtin, salannin, nimbin, and 6-desacetylnimbin on ecdysone 20-monooxygenase activity. Arch Insect Biochem 1997; 35: 199–209

[107] Ekong DEU. Chemistry of the meliacins (limonoids). The structure of nimbolide, a new meliacin from *Azadirachta indica*. Chem Commun (London) 1967; 16: 808

[108] Rojatkar SR, Bhat VS, Kulkarni MM, Joshi VS, Nagasampagi BA. Tetranortriterpenoids from *Azadirachta indica*. Phytochemistry 1989; 28: 203–205

[109] Momchilova S, Antonova D, Marekov I, Kuleva L, Damyanova BN, Jhamb G. Fatty acids, triacylglycerols, and sterols in neem oil (*Azadirachta indica* A. Juss) as determined by a combination of chromatographic and spectral techniques. J Liq Chrom Rel Technol 2007; 30: 111–125

[110] Choi JM, Lee EO, Lee HJ, Kim KH, Ahn KS, Shim BS, Kim NI, Song MC, Baek NI, Kim SH. Identification of campesterol from *Chrysanthemum coronarium* L. and its antiangiogenic activities. Phytother Res 2007; 21: 954–959

[111] Villaseñor IM, Angelada J, Canlas AP, Echegoyen D. Bioactivity studies on beta-sitosterol and its glucoside. Phytother Res 2002; 16: 417–421

[112] Khanavi M, Gheidarloo R, Sadati N, Ardekani MR, Nabavi SM, Tavajohi S, Ostad SN. Cytotoxicity of fucosterol containing fraction of marine algae against breast and colon carcinoma cell line. Pharmacogn Mag 2012; 8: 60–64

[113] Zhong PU, Zhang Y, Zhong YIN, Jiao XU, Ren JIA, Yang LU, Yang F. Antibacterial activity of 9-octadecanoic acid-hexadecanoic acid-tetrahydrofuran-3,4-diyl ester from neem oil. Agric Sci China 2010; 9: 1236–1240

[114] Kikuchi T, Ishii K, Noto T, Takahashi A, Tabata K, Suzuki T, Akihisa T. Cytotoxic and apoptosis-inducing activities of limonoids from the seeds of *Azadirachta indica* (neem). J Nat Prod 2011; 74: 866–870

[115] Kraus W. Biologically active compounds from Meliaceae. Stud Org Chem 1984; 17: 331–345

[116] Siddiqui S, Ghiasuddin, Siddiqui SB, Faizi S. Tetranortriterpenoids and steroidal glycosides from the seeds of *Azadirachta indica*. Pak J Sci Ind Res 1989; 32: 435

[117] Devakumar C, Mukerjee SK. 4-Epi nimbin, a new meliacin from *Azadirachta indica* A. Juss. Indian J Chem 1985; 24B: 1105

[118] Bokel M, Cramer R, Gutzeit H, Reeb S, Kraus W. Tetranortriterpenoids related to nimbin and nimbolide from *Azadirachta indica* A. Juss (Meliaceae). Tetrahedron 1990; 46: 775–782

[119] Cohen E, Ouistad GB, Jefferies PR, Casida JE. Nimbolide is the principal cytotoxic component of neem-seed insecticide preparations. Pestic Sci 1996; 48: 135–140

[120] Priyadarsini RV, Murugan RS, Sripriya P, Karunagaran D, Nagini S. The neem limonoids azadirachtin and nimbolide induce cell cycle arrest and mitochondria-mediated apoptosis in human cervical cancer (HeLa) cells. Free Radic Res 2010; 44: 624–634

[121] Chen J, Chen J, Sun Y, Yan Y, Kong L, Li Y, Qiu M. Cytotoxic triterpenoids from *Azadirachta indica*. Planta Med 2011; 77: 1844–1847

[122] Elumalai P, Gunadharini DN, Senthilkumar K, Banudevi S, Arunkumar R, Benson CS, Sharmila G, Arunakaran J. Induction of apoptosis in human breast cancer cells by nimbolide through extrinsic and intrinsic pathway. Toxicol Lett 2012; 215: 131–142

[123] Kigodi PG, Blaskó G, Thebtaranonth Y, Pezzuto JM, Cordell GA. Spectroscopic and biological investigation of nimbolide and 28-deoxonimbolide from *Azadirachta indica*. J Nat Prod 1989; 52: 1246–1251

[124] Ochi M, Kotsuki H, Kataoka T, Tada T, Tokoroyama T. Limonoids from *Melia azedarach* Linn Var. Japonica makino III. The structure of ochinal and ochinin. Chem Lett 1978; 4: 331

[125] Butterworth JH, Morgan ED. Isolation of a substance that supresses feeding in locust. J Chem Soc Chem Commun 1968: 23–24

[126] Morgan ED, Thornton MD. Azadirachtin in the fruit of *Melia azedarach*. Phytochemistry 1973; 12: 391–392

[127] Kraus W. Constituents of neem and related species. A revised structure of azadirachtin. Stud Org Chem (Amsterdam) 1986; 26: 237–256

[128] Rembold H, Forster H, Sonnebichller J. Structure of azadirachtin B. Z Naturforch 1989; 42C: 4–6

[129] Rojatkar SR, Nagasampagi BA. *a*-acetoxy-1*a*-hydroxyazadirachtol, a new constituent from *Azadirachta indica* (A. Juss.) seeds. Indian J Chem 1995; 34B: 1016–1018

[130] Rojatkar SR, Nagasampagi BA. 11α-hydroxy-12-norazadirachtin from *Azadirachta indica* (A. Juss.). Nat Prod Lett 1994; 5: 6976

[131] Govindachari TR, Sandhya G, Ganeshraj SP. Isolation of novel azadirachtins H and I by high performance liquid chromatography. Chromatographia 1991; 31: 303–305

[132] Govindachari TR, Gopalakrishnan G, Suresh G. Isolation of various azadirachtins from neem oil by preparative high performance liquid chromatography. J Liq Chrom Rel Technol 1996; 19: 1729–1733

[133] Govindachari TR, Sandhya G, Ganeshraj SP. Azadirachtin H and I: two new tetranortriterpenoids from *Azadirachta indica*. J Nat Prod 1992; 55: 596–601

[134] Garg HS, Bhakuni DS. Salannolide, a meliacin from *Azadirachta indica*. Phytochemistry 1984; 23: 2383–2385

[135] Kraus W, Baumann S, Bokel M, Cramer R, Grimminger W, Hendlemeir R, Keil E, Keller U, Klenk A, Klingele MPH, Schwinger M. Insect feeding and development controlling constituents of Meliaceae. In: Proc Ist Princess Chulabhorn Sci Cong, Ist Cong on Nat Prod Bangkok, vol 2; 1987: 554

[136] Kumar CS, Srinivas M, Yakkundi S. Limonoids from the seeds of *Azadirachta indica*. Phytochemistry 1996; 43: 451–455

[137] Bilton JN, Broughton HB, Jones PS, Ley SV, Rzepa HS, Sheppard RN, Slawin AMZ, Williams DJ, Lidert Z, Morgan ED. An x-ray crystallographic, mass spectroscopic, and NMR study of the limonoid insect antifeedant azadirachtin and related derivatives. Tetrahedron 1987; 43: 2805–2815

[138] Govindachari TR, Sandhya G, Ganeshraj SP. Structure of azadirachtin K, a new tetranortriterpenoid from *Azadirachta indica*. Indian J Chem 1992; 31B: 295–298

[139] Ramji N, Venkatakrishnan K, Madyastha KM. 11-epi-azadirachtin H from *Azadirachta indica*. Phytochemistry 1996; 42: 561

[140] Rojatkar SR, Nagasampagi BA. 1-tigloyl-3-acetyl-11-hydroxy-4β-methylmeliacarpin from *Azadirachta indica*. Phytochemistry 1992; 32: 213–214

[141] Ramji N, Venkatakrishnan K, Madyastha KM. 11-epi-azadirachtin D: an epimeric azadirachtin analogue from *Azadirachta indica*. Phytochemistry 1998; 49: 265–267

[142] Mitra CR, Garg HS, Pandey GN. Constituents of *Melia indica*-II nimbidic acid and nimbidinin. Tetrahedron Lett 1970; 11: 2761–2764

[143] Mitra CR, Garg HS, Pandey GN. Identification of nimbidic and nimbidinin from *Azadirachta indica*. Phytochemistry 1970; 10: 857

[144] Akhila A, Srivastava M, Rani K. Production of radioactive azadirachtin in the seed kernels of *Azadirachta indica*. J Nat Prod 1998; 11: 107–110

[145] Luo X, Ma Y, Wu S, Wu D. Two novel azadirachtin derivatives from *Azadirachta indica*. J Nat Prod 1999; 62: 1022–1024

[146] Klenk A, Bokel M, Kraus W. 3-Tigloylazadirachtol (tigloyl-2-methylcrotonoyl), an insect growth regulating constituent of *Azadirachta indica*. J Chem Soc Chem Commun 1986: 523–524

[147] Bilton JN, Jones PS, Ley SV, Robinson NG, Sheppard RN. Chemistry of insect antifeedants from *Azadirachta indica*. Part I: Conversion from the azadirachtin to the azadirachtinin skeletons. Tetrahedron Lett 1988; 29: 1849–1852

[148] Govindachari TR, Gopalakrishnan G, Suresh G. Purification of azadirachtin-B (3-tigloylazadirachtol) by preparative high performance liquid chromatography, using the recycling mode. J Liq Chrom Rel Technol 1997; 20: 1633–1636

[149] Grimalt S, Thompson DG, Coppens M, Chartrand DT, Shorney T, Meating J, Scarr T. Analytical study of azadirachtin and 3-tigloylazadirachtol residues in foliage and phloem of hardwood tree species by liquid chromatography-electrospray mass spectrometry. J Agric Food Chem 2011; 59: 8070–8077

[150] Govindachari TR, Gopalakrishnan G. 13,14-desepoxy-azadirachtin-A, a tetranortriterpenoid from *Azadirachta indica*. Phytochemistry 1997; 45: 397–399

[151] Kraus W, Klenk A, Bokel M, Vogler B. Tetranortriterpenoid lactams with insect antifeeding activity from *Azadirachta indica* A. Juss (Meliaceae). Liebig Ann Chem 1987; 4: 337–340

[152] Siddiqui S, Mahmood T, Siddiqui BS, Faizi S. Triterpenoids from kernel of *Azadirachta indica*. Proc Pak Acad Sci 1990; 27: 333–348

[153] Ghiasuddin. Chemical studies on the constituents of *Azadirachta indica* A. Juss. [Ph.D. Dissertation]. Karachi: University of Karachi; 1993

[154] Wang HW, Liu JQ, Chen JX, Yang YF, Yan YX, Li ZR, Qiu MH. New triterpenoids from the kernels of *Azadirachta indica*. Nat Prod Bioprospect 2013; 3: 33–37

[155] Mc Inerney BV, Taylor WC. The Xenocoumarins and related biologically active Dihydroisocoumarins. In: Rahman A, ed. Studies in natural Products Chemistry, Vol 15. Elsevier: Amsterdam; 1995: 381–422

[156] Kurosaki F, Nishi A. Isolation and antimicrobial activity of the phytoalexin 6-methoxymellein from cultured carrot cells. Phytochemistry 1983; 22: 669–672

[157] Borris RP, Cordell GA, Farnsworth NR. Isofraxidin, a cytotoxic coumarin from *Micrandra elata* (Euphorbiaceae). J Nat Prod 1980; 43: 641–643

[158] Siddiqui S, Mahmood T, Siddiqui BS, Faizi S. Isonimolide and isonimbolide, two new tetranortriterpenoids from the twigs of *Azadirachta indica* A. Juss (Meliaceae). Heterocycles 1987; 26: 1827–1833

[159] Siddiqui S, Faizi S, Mahmood T, Siddiqui BS. Margosinolide and isomargosinolide, two new tetranortriteprenoids from *Azadirachta indica* A. Juss (Meliaceae). Tetrahedron 1986; 42: 4849–4856

[160] Siddiqui S, Mahmood T, Siddiqui BS, Faizi S. Two new tetranortriterpenoids from *Azadirachta indica*. J Nat Prod 1986; 49: 1068–1073

[161] Ara I, Siddiqui BS, Faizi S, Siddiqui S. Three new diterpenoids from the stem bark of *Azadirachta indica*. J Nat Prod 1990; 53: 816–820

[162] Ara I, Siddiqui BS, Faizi S, Siddiqui S. Structurally novel diterpenoid constituents from the stem bark of *Azadirachta indica*. J Chem Soc Perkin Trans I 1989: 343–345

[163] Ara I, Siddiqui BS, Faizi S, Siddiqui S. Tricyclic diterpenes from the stem bark of *Azadirachta indica*. Planta Med 1990; 56: 84–86

[164] Ara I, Siddiqui BS, Faizi S, Siddiqui S. Tricyclic diterpenoids from the stem bark of *Azadirachta indica*. J Nat Prod 1988; 51: 1054–1061

[165] Ara I, Siddiqui BS, Faizi S, Siddiqui S. Terpenoids from the stem bark of *Azadirachta indica*. Phytochemistry 1988; 27: 1801–1804

[166] Siddiqui S, Ara I, Faizi S, Mahmood T, Siddiqui BS. Phenolic tricyclic diterpenoids from the bark of *Azadirachta indica*. Phytochemistry 1988; 27: 3903–3907

[167] Ara I, Siddiqui BS, Faizi S, Siddiqui S. Diterpenoids from the stem bark of *Azadirachta indica*. Phytochemistry 1989; 28: 1177–1180

[168] Sengupta P, Choudhuri SN, Khastgir HN. Investigations of the trunk bark of *Melia azadirachta*. Linn Chem and Ind (London) 1958; 1958: 861–862

[169] Sengupta P, Chowdhury SN, Khastagir HN. Terpenoids and related compounds – I. Constituents of the trunk bark of *Melia azadirachta* Linn and the structure of the ketophenol, nimbiol. Tetrahedron 1960; 10: 45–54

[170] Sengupta P, Sengupta SK, Khastgir HN. Terpenoids and related compounds – II Investigations on the structure of nimbin. Tetrahedron 1960; 11: 67–77

[171] Choudhuri SN, Khastgir HN, Sengupta P. Investigation on the structure of Nimbiol. Chem and Ind (London) 1959; 20: 634–635

[172] Chao KP, Hua KF, Hsu HY, Su YC, Chang ST. Anti-inflammatory activity of sugiol, a diterpene isolated from *Calocedrus formosana* bark. Planta Med 2005; 71: 300–305

[173] Ara I, Siddiqui BS, Faizi S, Siddiqui S. Margosinone and margosinolone, two new polyacetate derivatives from *Azadirachta indica*. Fitoterapia 1989; 60: 519–523

[174] Banerji R, Misra G, Nigam SK. Identification of 24-methylene lophenol from heartwood of *Azadirachta indica*. Phytochemistry 1987; 26: 2644–2645

[175] Ekong DEU, Fakunle CO, Fasina AK, Okogun JI. The meliacins (limonoids). Nimbolin A and B, two new meliacin cinnamates from *Azadirachta indica* L. and *Melia azedarach* L. J Chem Soc D, Chem Commun 1969; 20: 1166–1167

[176] Nakatani M. Limonoids from Meliaceae and their biological Activities. In: Tringali C, ed. Bioactive Compounds from Natural Sources – Isolation, Characterisation and biological Properties. Boca Raton: Taylor and Francis; 2000: 527–554

[177] Van der Nat JM, van der Sluis WG, 't Hart LA, Van Dijk H, de Silva KT, Labadie RP. Activity-guided isolation and identification of *Azadirachta indica* bark extract constituents which specifically inhibit chemiluminescence production by activated human polymorphonuclear leukocytes. Planta Med 1991; 57: 65–68

[178] Yang B, Kotani A, Arai K, Kusu F. Estimation of the antioxidant activities of flavonoids from their oxidation potentials. Anal Sci 2001; 17: 599–604

[179] Miyazawa M, Shimamura H, Nakamura S. Antimutagenic activity of isofraxinellone from *Dictamnus dasycarpus*. J Agric Food Chem 1995; 43: 1428–1431

[180] Banerji B, Nigam SK. Wood constituents of Meliaceae: a review. Fitoterapia 1984; 55: 3–36

[181] Simmonds MSJ, Jarvis AP, Johnson S, Jones GR, Morgan ED. Comparison of anti-feedant and insecticidal activity of nimbin and salannin photo-oxidation products with neem (*Azadirachta indica*) limonoids. Pest Manag Sci 2004; 60: 459–464

[182] Ara I. Studies in the chemical constituents of *Azadirachta indica* (neem) [Ph.D. Dissertation]. Karachi: University of Karachi; 1989

[183] Ara I, Siddiqui BS, Faizi S, Siddiqui S. Isolation and structure elucidation of the triterpene azadirinin from the roots of *Azadirachta indica*. Fitoterapia 1992; 63: 118

[184] Ara I, Siddiqui BS, Faizi S, Siddiqui S. Tricyclic diterpenoids from root bark of *Azadirachta indica*. Phytochemistry 1990; 29: 911–914

[185] Majumder PL, Maiti DC, Kraus W, Bokel M. Nimbidiol, a modified diterpenoid of the root-bark of *Azadirachta indica*. Phytochemistry 1987; 26: 3021–3023

[186] Ekong DEU, Olagbemi EO, Spiff AI. Cycloeucalenol and 24-methylenecycloartanol in wood oils from the family Meliaceae. Chem Ind (London) 1968; 1968: 1808

[187] Kiribuchi M, Miura K, Tokuda S, Kaneda T. Hypocholesterolemic effect of triterpene alcohols with soysterol on plasma cholesterol in rats. J Nutr Sci Vitaminol (Tokyo) 1983; 29: 35–43

[188] Mukherjee S, Srivastava HC. Structure of neem gum. J Am Chem Soc 1955; 77: 422

[189] Anderson DMW, Hendrie A. The proteinaceous gum polysacheride from *Azadirachta indica*. Carbohyd Res 1979; 20: 259–268

[190] Lakshmi SU, Pattabiraman TN. Studies on the plant gum: Part I. Identification of nitrogenous compounds in neem (*Azadirachta indica*) gum and isolation of D-glucosamin. Indian J Biochem 1967; 4: 183

[191] Bajpai KS, Chandrasekharan V, Mukherjee S, Srivastava AN. Isolation of pure aldobiouronie and aldotriouronic acid from the roots of *Azadirachta indica*. Fitoterapia 1970; 63: 118

[192] Lavie D, Jain MK. Tetranortriterpenoids from *Melia azadirachta* L. Chem Commun 1967: 278–280

[193] Akhila A, Rani K. Chemistry of the neem tree (*Azadirachta indica* A. Juss.). Fortschr Chem Org Naturst 1999; 78: 47–149

[194] Madhusudanan KP, Chaturvedi R, Garg HS, Bhakuni DS. Negative ion mass spectra of tetranortriterpenoids isolated from neem (*Azadirachta indica* A. Juss.). Indian J Chem Sect B 1984; 23: 1082

[195] Gossé B, Amissa AA, Adjé FA, Niamké FB, Ollivier D, Ito Y. Analysis of components of neem (*Azadirachta indica*) oil by diverse chromatographic techniques. J Liq Chrom Rel Technol 2005; 28: 14, 2225–2233

[196] Rizvi SH, Kapil RS, Shoeb A. Alkaloids and coumarins of *Casimiroa edulis*. J Nat Prod 1985; 48: 146

[197] Mitra C. On the constitution of nimbin. J Sci Ind Res (India) 1957; 16 B: 477

[198] Sadeghian MM, Mortazaienezhad F. Investigation of compounds from *Azadirachta indica* (neem). Asian J Plant Sci 2007; 6: 444–445

[199] Lavie D, Jain MK, Shpan-Gabrielith SR. A locust phagorepellent from two melia species. Chem Commun 1967: 910–911

[200] Garg HS, Bhakuni DS. An isoprenylated flavanone from leaves of *Azadirachta indica*. Phytochemistry 1984; 23: 2115–2118

[201] Panda S, Kar A. Evaluation of the antithyroid, antioxidative and antihyperglycemic activity of scopoletin from *Aegle marmelos* leaves in hyperthyroid rats. Phytother Res 2006; 20: 1103–1105

[202] Rukmini C. Chemical and nutritional evaluation of neem oil. Food Chem 1987; 26: 119–124

[203] Devakumar C, Mukerjee SK. Chemistry of neem bitter principles. IARI Research Bulletin 1983; 40: 1–17

[204] Yamasaki RB, Klocke JA. Structure-bioactivity relationships of azadirachtin, a potent insect control agent. J Agric Food Chem 1987; 35: 467–471

[205] Sankaram AVB, Murthy MM, Bhaskariah K, Subramany M, Sultana N, Sharma HC, Leischner K. 16th International Symposium on the Chemistry of Natural Products. IUPAC, Japan: Kyoto, Abs. No 1539; 1988: 41

[206] Teng BS, Lu YH, Wang ZT, Tao XY, Wei DZ. *In vitro* anti-tumor activity of isorhamnetin isolated from *Hippophae rhamnoides* L. against BEL-7402 cells. Pharmacol Res 2006; 54: 186–194

[207] Goel RK, Pandey VB, Dwivedi SP, Rao YV. Antiinflammatory and antiulcer effects of kaempferol, a flavone, isolated from *Rhamnus procumbens*. Indian J Exp Biol 1988; 26: 121–124

[208] Pekkarinen SS, Heinonen IM, Hopia AI. Flavonoids quercetin, myricetin, kaemferol and (+)-catechin as antioxidants in methyl linoleate. J Sci Food Agric 1999; 79: 499–506

[209] Kaur G, Sarwar Alam M, Athar M. Nimbidin suppresses functions of macrophages and neutrophils: relevance to its antiinflammatory mechanisms. Phytother Res 2004; 18: 419–424

[210] Mosaddek ASM, Rashid MMU. A comparative study of the anti-inflammatory effect of aqueous extract of neem leaf and dexamethasone. Bangladesh J Pharmacol 2008; 3: 44–47

[211] Mahabub-Uz-Zaman M, Ahmed NU, Akter R, Ahmed K, Aziz MSI, Ahmed MS. Studies on anti-inflammatory, antinociceptive and antipyretic activities of ethanol extract of *Azadirachta indica* leaves. Bangladesh J Sci Ind Res 2009; 44: 199–206

[212] Upadhyay SN, Dhawan S, Garg S, Talwar GP. Immunomodulatory effects of neem (*Azadirachta indica*) oil. Int J Immunopharmacol 1992; 14: 1187–1193

[213] SaiRam M, Sharma SK, Ilavazhagan G, Kumar D, Selvamurthy W. Immunomodulatory effects of NIM-76, a volatile fraction from neem oil. J Ethnopharmacol 1997; 55: 133–139

[214] Kumar A, Rao AR, Kimura H. Radiosensitizing effects of neem (*Azadirachta indica*) oil. Phytother Res 2002; 16: 74–77

[215] Bopanna KN, Kannan J, Sushma G, Balaraman R, Rathod SP. Antidiabetic and antihyperlipaemic effects of neem seed kernel powder on alloxan diabetic rabbits. Indian J Pharmacol 1997; 29: 162–167

[216] Bajaj S, Srinivasan BP. Investigations into the anti-diabetic activity of *Azadirachta indica*. Indian J Pharmacol 1999; 31: 138–141

[217] Halim EM. Lowering of blood sugar by water extract of *Azadirachta indica* and *Abroma augusta* in diabetes rats. Indian J Exp Biol 2003; 41: 636–640

[218] Ebong PE, Atangwho IJ, Eyong EU, Egbung GE. The antidiabetic efficacy of combined extracts from two continental plants: *Azadirachta indica* (A. Juss) (neem) and *Vernonia amygdalina* (Del.) (african bitter leaf). Am J Biochem Biotechnol 2008; 4: 239–244

[219] Bisht S, Sisodia SS. Anti-hyperglycemic and antidyslipidemic potential of *Azadirachta indica* leaf extract in STZ-induced diabetes mellitus. J Pharma Sci Res 2010; 2: 622–627

[220] Dholi SK, Raparla R, Mankala SK, Nagappan K. *In vivo* antidiabetic evaluation of neem leaf extract in alloxan induced rats. J App Pharma Sci 2011; 1: 100–105

[221] Garg GP, Nigam SK, Ogle CW. The gastric antiulcer effects of the leaves of the neem tree. Planta Med 1993; 59: 215–217

[222] Chattopadhyay I, Nandi B, Chatterjee R, Biswas K, Bandyopadhyay U, Banerjee RK. Mechanism of antiulcer effect of neem (*Azadirachta indica*) leaf extract: effect on H+-K+-ATPase, oxidative damage and apoptosis. Inflammopharmacology 2004; 12: 153–176

[223] Upadhyay SN, Kaushic C, Talwar GP. Antifertility effects of neem (*Azadirachta indica*) oil by single intrauterine administration: a novel method for contraception. Proc Biol Sci 1990; 242: 175–179

[224] Upadhyay SN, Dhawan S, Talwar GP. Antifertility effects of neem (*Azadirachta indica*) oil in male rats by single intra-vas administration: an alternate approach to vasectomy. J Androl 1993; 14: 275–281

[225] Sharma SK, SaiRam M, Ilavazhagan G, Devendra K, Shivaji SS, Selvamurthy W. Mechanism of action of NIM-76: a novel vaginal contraceptive from neem oil. Contraception 1996; 54: 373–378

[226] Riar SS, Devakumar C, Sawhney RC, Ilavazhagan G, Bardhan J, Kain AK, Thomas P, Singh R, Singh B, Parshad R. Antifertility activity of volatile fraction of neem oil. Contraception 1991; 44: 319–326

[227] Khillare B, Shrivastav TG. Spermicidal activity of *Azadirachta indica* (neem) leaf extract. Contraception 2003; 68: 225–229

[228] Khalid SA, Duddeck H, Gonzales-Sierra M. Isolation and characterization of an antimalarial agent of the neem tree *Azadirachta indica*. J Nat Prod 1989; 52: 922–927

[229] Vasanth S, Gopal RH, Rao RH, Rao RB. Plant antimalarial agents. J Sci Ind Res 1990; 49: 68–77

[230] Schwikkard S, van Heerden FR. Antimalarial activity of plant metabolites. Nat Prod Rep 2002; 19: 675–692

[231] Lucantoni L, Yerbanga RS, Lupidi G, Pasqualini L, Esposito F, Habluetzel A. Transmission blocking activity of a standardized neem (*Azadirachta indica*) seed extract on the rodent malaria parasite *Plasmodium berghei* in its vector *Anopheles stephensi*. Malaria J 2010; 9: 66

[232] Udeinya IJ, Mbah AU, Chijioke CP, Shu EN. An anti-malarial extract from neem leaves is antiretroviral. Trans Royal Soc Trop Med Hyg 2004; 98: 435–437

[233] Mbah AU, Udeinya IJ, Shu EN, Chijioke CP, Nubila T, Udeinya F, Muobuike A, Mmuobieri A, Obioma MS. Fractionated neem leaf extract is safe and increases CD4+ cell levels in HIV/AIDS patients. Am J Ther 2007; 14: 369–374

[234] Khan MI, Shah NH. Antifungal activity of leaf extract of neem on seed mycoflora of wheat. Bioved 1992; 3: 209–210

[235] Suresh G, Narasimhan NS, Masilamani S, Partho PD, Gopalakrishnan G. Antifungal fractions and compounds from uncrushed green leaves of *Azadirachta indica*. Phytoparasitica 1997; 25: 33–39

[236] Govindachari TR, Suresh G, Geetha G, Banumathy B, Masilamani S. Identification of antifungal compounds from the seed oil of *Azadirachta indica*. Phytopathology 1998; 26: 109–116

[237] Natarajan V, Venugopal PV, Menon T. Effect of *Azadirachta indica* (neem) on the growth pattern of dermatophytes. Indian J Med Microbiol 2003; 21: 98–101

[238] Wang J, Li J, Cao J, Jiang W. Antifungal activities of neem (*Azadirachta indica*) seed kernel extracts on postharvest diseases in fruits. Afr J Microbiol Res 2010; 4: 1100–1104

[239] Das BK, Mukherjee SC, Sahu BB, Murjani G. Neem (*Azadirachta indica*) extract as an antibacterial agent against fish pathogenic bacteria. Indian J Exp Biol 1999; 37: 1097–1100

[240] SaiRam M, Ilavazhagan G, Sharma SK, Dhanraj SA, Suresh B, Parida MM, Jana AM, Devendra K, Selvamurthy W. Anti-microbial activity of a new vaginal contraceptive NIM-76 from neem oil (*Azadirachta indica*). J Ethnopharmacol 2000; 71: 377–382

[241] Coventry E, Allan EJ. Microbiological and chemical analysis of neem (*Azadirachta indica*) extracts: new data on antimicrobial activity. Phytoparasitica 2001; 29: 441–450

[242] Vanka A, Tandon S, Rao SR, Udupa N, Ramkumar P. The effect of indigenous neem *Azadirachta indica* mouth wash on *Streptococcus mutans* and *Lactobacilli* growth. Indian J Dent Res 2001; 12: 133–144

[243] Pai MR, Acharya LD, Udupa U. Evaluation of antiplaque activity of *Azadirachta indica* leaf extract gel-a 6-week clinical study. J Ethnopharmacol 2004; 90: 99–103

[244] Joshi M, Ali SW, Rajendran S. Antibacterial finishing of polyester/cotton blend fabrics using neem (*Azadirachta indica*): a natural bioactive agent. J Appl Polym Sci 2007; 106: 793–800

[245] Jahan T, Begum ZA, Sultana S. Effect of neem oil on some pathogenic bacteria. Bangladesh J Pharmacol 2007; 2: 71–72

[246] Matthews RL, Templeton MR, Tripathi SK, Bhattarai K. Disinfection of waterborne coliform bacteria by neem oil. Environ Eng Sci 2009; 26: 1435–1441

[247] Aslam F, Rehman K, Asghar M, Sarwar M. Antibacterial activity of various phytoconstituents of neem. Pak J Agri Sci 2009; 46: 209–213

[248] Zhang YQ, Xu J, Yin ZQ, Jia RY, Lu Y, Yang F, Du YH, Zou P, Lv C, Hu TX, Liu SL, Shu G, Yi G. Isolation and identification of the antibacterial active compound from petroleum ether extract of neem oil. Fitoterapia 2010; 81: 747–750

[249] Maragathavalli S, Brindha S, Kaviyarasi NS, Annadurai B, Gangwar SK. Antimicrobial activity in leaf extract of neem (*Azadirachta indica* Linn.). Int J Sci Nature 2012; 3: 110–113

[250] Lowery DT, Eastwell KC, Smirle MJ. Neem seed oil inhibits aphid transmission of potato virus Y to pepper. Ann Appl Biol 1997; 130: 217–225

[251] Badman L, Joshi SP, Bedekar SS. *In vitro* antiviral activity of neem (*Azadirachta indica,* A. Juss) leaf extract against coxsachieviruses. J Commun Dis 1999; 31: 79–90

[252] Parida MM, Upadhyay C, Pandya G, Jana AM. Inhibitory potential of neem (*Azadirachta indica* Juss) leaves on dengue virus type-2 replication. J Ethnopharmacol 2002; 79: 273–278

[253] Tiwari V, Darmani NA, Yue BY, Shukla D. In vitro antiviral activity of neem (*Azardirachta indica* L.) bark extract against herpes simplex virus type-1 infection. Phytother Res 2010; 24: 1132–1140

[254] Amer H, Helmy WA, Taie HAA. *In vitro* antitumor and antiviral activities of seeds and leaves neem (*Azadirachta indica*) extracts. Int J Acad Res 2010; 2: 47–51

[255] Nanduria S, Thunuguntlaa SSR, Nyavanandia VK, Kasua S, Kumara MP, Rama PS, Rajagopalb S, Kumarb RA, Deevib DS, Rajagopalanb R, Venkateswarlua A. Biological investigation and structure-activity relationship studies on azadirone from *Azadirachta indica* A. Juss. Bioorg Med Chem Lett 2003; 13: 4111–4115

[256] Balasenthil S, Arivazhagan S, Ramachandran CR, Ramachandran V, Nagini S. Chemopreventive potential of neem (*Azadirachta indica*) on 7,12-dimethylbenz[a]anthracene (DMBA) induced hamster buccal pouch carcinogenesis. J Ethnopharmacol 1999; 67: 189–195

[257] Subapriya R, Kumaraguruparan R, Chandramohan KV, Nagini S. Chemoprotective effects of ethanolic extract of neem leaf against MNNG-induced oxidative stress. Pharmazie 2003; 58: 512–517

[258] Dasgupta T, Banerjee S, Yadava PK, Rao AR. Chemopreventive potential of *Azadirachta indica* (neem) leaf extract in murine carcinogenesis model systems. J Ethnopharmacol 2004; 92: 23–36

[259] Subapriya R, Bhuvaneswari V, Nagini S. Ethanolic neem (*Azadirachta indica*) leaf extract induces apoptosis in the hamster buccal pouch carcinogenesis model by modulation of Bcl-2, Bim, caspase 8 and caspase 3. Asian Pac J Cancer Prev 2005; 6: 515–520

[260] Arakaki J, Suzui M, Morioka T, Kinjo T, Kaneshiro T, Inamine M, Sunagawa N, Nishimaki T, Yoshimi N. Antioxidative and modifying effects of a tropical plant *Azadirachta indica* (neem) on azoxymethane-induced preneoplastic lesions in the rat colon. Asian Pac J Cancer Prev 2006; 7: 467–471

[261] Roy MK, Kobori M, Takenaka M, Nakahara K, Shinmoto H, Isobe S, Tsushida T. Antiproliferative effect on human cancer cell lines after treatment with nimbolide extracted from an edible part of the neem tree (*Azadirachta indica*). Phytother Res 2007; 21: 245–250

[262] Vijayan V, Meshram GP. Genotoxicity assessment of NIM-76 and its formulation (pessary) in an *in vitro* Ames Salmonella/microsome assay and in vivo mouse bone marrow micronucleus test. Drug Chem Toxicol 2013; 36: 430–434

[263] Mallick A, Barik S, Goswami KK, Banerjee S, Ghosh S, Sarkar K, Bose A, Baral R. Neem leaf glycoprotein activates CD8(+) T cells to promote therapeutic anti-tumor immunity inhibiting the growth of mouse sarcoma. PLoS One 2013; 8: e47434. doi:10.1371/journal.pone.0047434

[264] Mallick A, Ghosh S, Banerjee S, Majumder S, Das A, Mondal B, Barik S, Goswami KK, Pal S, Laskar S, Sarkar K, Bose A, Baral R. Neem leaf glycoprotein is nontoxic to physiological functions of Swiss mice and Sprague-Dawley rats: histological, biochemical and immunological perspectives. Int Immunopharmacol 2013; 15: 73–83

[265] Srivastava P, Yadav N, Lella R, Schneider A, Jones A, Marlowe T, Lovett G, O'Loughlin K, Minderman H, Gogada R, Chandra D. Neem oil limonoids induces p53-independent apoptosis and autophagy. Carcinogenesis 2012; 33: 2199–2207

[266] Kale BP, Kothekar MA, Tayade HP, Jaju JB, Mateenuddin M. Effect of aqueous extract of *Azadirachta indica* leaves on hepatotoxicity induced by antitubercular drugs in rats. Indian J Pharmacol 2003; 35: 177–180

[267] Chattopadhyay RR, Bandyopadhyay M. Possible mechanism of hepatoprotective activity of *Azadirachta indica* leaf extract against paracetamol-induced hepatic damage in rats: Part III. Indian J Pharmacol 2005; 37: 184–185

[268] Mohamed ET, Mahran HA, Mahmoud MS. Hepato ameliorative effect of *Azadirachta indica* leaves extract against mercuric chloride environmental pollution. J Am Sci 2010; 6: 735–751

[269] Sithisarn P, Supabphol R, Gritsanapan W. Comparison of free radical scavenging activity of Siamese neem tree (*Azadirachta indica* A. Juss var. *siamensis* Valeton) leaf extracts prepared by different methods of extraction. Med Princ Pract 2006; 15: 219–222

[270] Ghimeray AK, Jin CW, Ghimire BK, Cho DH. Antioxidant activity and quantitative estimation of azadirachtin and nimbin in *Azadirachta Indica* A. Juss grown in foothills of Nepal. Afr J Biotechnol 2009; 8: 3084–3091

[271] Jaiswal AK, Bhattacharya SK, Acharya SB. Anxiolytic activity of *Azadirachta indica* leaf extract in rats. Indian J Exp Biol 1994; 32: 489–491

[272] Samad N, Parveen T, Haider S, Haleem DJ. Attenuation of stress-induced behavioural deficits by *Azadirachta indica* (neem): role of serotonin. Pak J Bot 2006; 38: 131–138

[273] Hiremath SB, Srinivas LD. A study on anxiolytic activity of *Azadirachta indica* leaves in wistar albino rats. Int J Adv Pharma Res 2011; 2: 563–568

[274] Singh K, Singh A, Singh DK. Molluscicidal activity of neem (*Azadirachta indica* A. Juss). J Ethnopharmacol 1996; 52: 35–40

[275] Ebenso IE. Molluscicidal effects of neem (*Azadirachta indica*) extracts on edible tropical land snails. Pest Manag Sci 2004; 60: 178–182

[276] Rahuman AA, Gopalakrishnan G, Venkatesan P, Geetha K. Isolation and identification of mosquito larvicidal compound from *Abutilon indicum* (Linn.) Sweet. Parasitol Res 2008; 102: 981–988

[277] Djenontin TS, Wottoa VD, Avlessia F, Lozanob P, Sohounhlouéa DKC, Piochb D. Composition of *Azadirachta indica* and *Carapa procera* (Meliaceae) seed oils and cakes obtained after oil extraction. Ind Crops Prod 2012; 38: 39–45

[278] Dua VK, Pandey AC, Raghavendra K, Gupta A, Sharma T, Dash AP. Larvicidal activity of neem oil (*Azadirachta indica*) formulation against mosquitoes. Malaria J 2009; 8: 124

[279] Ghaffar FA, Semmler M. Efficacy of neem seed extract shampoo on head lice of naturally infected humans in Egypt. Parasitol Res 2007; 100: 329–332

[280] Du YH, Jia RY, Yin ZQ, Pu ZH, Chen J, Yang F, Zhang YQ, Lu Y. Acaricidal activity of extracts of neem (*Azadirachta indica*) oil against the larvae of the rabbit mite *Sarcoptes scabiei* var. *cuniculi in vitro*. Vet Parasitol 2008; 157: 144–148

[281] Deng Y, Shi D, Yin Z, Guo J, Jia R, Xu J, Song X, Lv C, Fan Q, Liang X, Shi F, Ye G, Zhang W. Acaricidal activity of petroleum ether extract of neem (*Azadirachta indica*) oil and its four fractions separated by column chromatography against *Sarcoptes scabiei* var. *cuniculi* larvae *in vitro*. Exp Parasitol 2012; 130: 475–477

[282] Du YH, Li JL, Jia RY, Yin ZQ, Li XT, Lv C, Ye G, Zhang L, Zhang YQ. Acaricidal activity of four fractions and octadecanoic acid-tetrahydrofuran-3,4-diyl ester isolated from chloroform extracts of neem (*Azadirachta indica*) oil against Sarcoptes scabiei var. cuniculi larvae *in vitro*. Vet Parasitol 2009; 163: 175–178

[283] Xu J, Fan QJ, Yin ZQ, Li XT, Du YH, Jia RY, Wang KY, Lv C, Ye G, Geng Y, Su G, Zhao L, Hu TX, Shi F, Zhang L, Wu CL, Tao C, Zhang YX, Shi DX. The preparation of neem oil microemulsion (*Azadirachta indica*) and the comparison of acaricidal time between neem oil microemulsion and other formulations *in vitro*. Vet Parasitol 2010; 169: 399–403

[284] Mishra V, Parveen N, Singhal KC, Khan NU. Antifilarial activity of *Azadirachta indica* on cattle filarial parasite *Setaria cervi*. Fitoterapia 2005; 76: 54–61

[285] Zanno P, Miura I, Nakanishi K, Elder DL. Letter: structure of the insect phagorepellent azadirachtin. Application of PRFT/CWD carbon-13 nuclear magnetic resonance. J Am Chem Soc 1975; 97: 1975–1977

[286] Jauch J. Total synthesis of azadirachtin – finally completed after 22 years. Angew Chem Int Ed Engl 2008; 47: 34–37

[287] Ley SV, Abad-Somovilla A, Anderson JC, Ayats C, Bänteli R, Beckmann E, Boyer A, Brasca MG, Brice A, Broughton HB, Burke BJ, Cleator E, Craig D, Denholm AA, Denton RM, Durand-Reville T, Gobbi LB, Göbel M, Gray BL, Grossmann RB, Gutteridge CE, Hahn N, Harding SL, Jennens DC, Jennens L, Lovell PJ, Lovell HJ, de la Puente ML, Kolb HC, Koot WJ, Maslen SL, McCusker CF, Mattes A, Pape AR, Pinto A, Santafianos D, Scott JS, Smith SC, Somers AQ, Spilling CD, Stelzer F, Toogood PL, Turner RM, Veitch GE, Wood A, Zumbrunn C. The synthesis of azadirachtin: a potent insect antifeedant. Chemistry 2008; 14: 10683–10704

[288] Veitch GE, Beckmann E, Burke BJ, Boyer A, Maslen SL, Ley SV. Synthesis of azadirachtin: a long but successful journey. Angew Chem Int Ed Engl 2007; 46: 7629–7632

[289] Prakash G, Bhojwani SS, Srivastava AK. Production of azadirachtin from plant tissue culture-state of the art and future prospects. Biotechnol Bioprocess Eng 2002; 7: 185–193

[290] Allan EJ, Eeswara JP, Jarvis AP, Mordue (Luntz) AJ, Morgan ED, Stuchbury T. Induction of hairy root cultures of *Azadirachta indica* A. Juss. and their production of azadirachtin and other important insect bioactive metabolites. Plant Cell Rep 2002; 21: 374–379

[291] Satdive RK, Fulzele DP, Eapen S. Enhanced production of azadirachtin by hairy root cultures of *Azadirachta indica* A. Juss by elicitation and media optimization. J Biotechnol 2007; 128: 281–289

[292] Rafiq M, Dahot MU. Callus and azadirachtin related limonoids production through *in vitro* culture of neem (*Azadirachta indica* A. Juss). Afr J Biotechnol 2010; 9: 449–453

[293] Srivastava P, Chaturvedi R. Increased production of azadirachtin from an improved method of androgenic cultures of a medicinal tree *Azadirachta indica* A. Juss. Plant Signal Behav 2011; 6: 974–981

[294] Kusari S, Verma VC, Lamshoeft M, Spiteller M. An endophytic fungus from *Azadirachta indica* A. Juss. that produces azadirachtin. World J Microbiol Biotechnol 2012; 28: 1287–1294

[295] Hawksworth DL. The variety of fungal-algal symbioses, their evolutionary significance, and the nature of lichens. Bot J Linn Soc 1988; 96: 3–20

[296] Li WC, Zhou J, Guo SY, Guo LD. Endophytic fungi associated with lichens in Baihua mountain of Beijing, China. Fungal Divers 2007; 25: 69–80

[297] Schulz B, Wanke U, Draeger S, Aust HJ. Endophytes from herbaceous plants and shrubs: effectiveness of surface sterilization methods. Mycol Res 1993; 97: 1447–1450

[298] Fisher PJ. Survival and spread of the endophyte *Stagonospora pteridiicola* in *Pteridium aquilinum*, other ferns and some flowering plants. New Phytol 1996; 132: 119–122

[299] Legault D, Dessureault M, Laflamme G. Mycoflore des aiguilles de *Pinus banksiana* et *Pinus resinosa* I. Champignons endophytes. Canadian J Bot 1989; 67: 2052–2060

[300] Kharwar RN, Gond SK, Kumar A, Mishra A. A comparative study of endophytic and epiphytic fungal association with leaf of *Eucalyptus citriodora* Hook. and their antimicrobial activity. World J Microbiol Biotechnol 2010; 26: 1941–1948

[301] Gond SK, Mishra A, Sharma VK, Verma SK, Kumar J, Kharwar RN, Kumar A. Diversity and antimicrobial activity of endophytic fungi isolated from *Nyctanthes arbor-tristis*, a well-known medicinal plant of India. Mycoscience 2012; 53: 113–121

[302] Rodrigues KF. Fungal Endophytes of Palms. In: Redlin SC, Carris LM, eds. Endophytic Fungi in Grasses and woody Plants: Systematics, Ecology and Evolution. St. Paul, Minnesota, USA: APS Press; 1996: 121–132

[303] Fröhlich J, Hyde KD, Petrini O. Endophytic fungi associated with palms. Mycol Res 2000; 104: 1202–1212

[304] Maria GL, Sridhar KR. Endophytic fungal assemblage of two halophytes from west coastal mangrove habitats, India. Czech Mycol 2003; 55: 241–251

[305] Suryanarayanan TS, Kumaresan V. Endophytic fungi of some halophytes from an estuarine mangrove forest. Mycol Res 2000; 104: 1465–1467

[306] Saikkonen K, Ahlholm J, Helander M, Lehtimäki S, Niemeläinen O. Endophytic fungi in wild and cultivated grasses in Finland. Ecography (Cop.) 2000; 23: 360–366

[307] Thirunavukkarasu N, Suryanarayanan TS, Girivasan KP, Venkatachalam A, Geetha V, Ravishankar JP, Doble M. Fungal symbionts of marine sponges from Rameswaram, southern India: species composition and bioactive metabolites. Fungal Divers 2012; 55: 37–46

[308] Zhang Y, Mu J, Feng Y, Kang Y, Zhang J, Gu PJ, Wang Y, Ma LF, Zhu YH. Broad-spectrum antimicrobial epiphytic and endophytic fungi from marine organisms: isolation, bioassay and taxonomy. Mar Drugs 2009; 7: 97–112

[309] Stone JK, Bacon CW, White JE. An Overview of endophytic Microbes: Endophytism defined. In: Bacon CW, White JF, eds. Microbial Endophytes. New York: Marcel Dekker Inc.; 2000: 3–29

[310] Verma VC, Gond SK, Kumar A, Kharwar RN, Strobel G. The endophytic mycoflora of bark, leaf, and stem tissues of *Azadirachta indica* A. Juss (neem) from Varanasi (India). Microb Ecol 2007; 54: 119–125

[311] Mishra A, Gond SK, Kumar A, Sharma VK, Verma SK, Kharwar RN, Sieber TN. Season and tissue type affect fungal endophyte communities of the Indian medicinal plant *Tinospora cordifolia* more strongly than geographic location. Microb Ecol 2012; 64: 388–398

[312] Gunatilaka AAL. Natural products from plant-associated microorganisms: distribution, structural diversity, bioactivity, and implication of their occurrence. J Nat Prod 2006; 69: 509–526

[313] Verma VC, Gond SK, Kumar A, Mishra A, Kharwar RN, Gange AC. Endophytic actinomycetes from *Azadirachta indica* A. Juss.: isolation, diversity, and anti-microbial activity. Microb Ecol 2009; 57: 749–756

[314] Kharwar RN, Verma VC, Kumar A, Gond SK, Harper JK, Hess WM, Lobkovosky E, Ma C, Ren Y, Strobel GA. Javanicin, an antibacterial naphthaquinone from an endophytic fungus of neem, *Chloridium* sp. Curr Microbiol 2009; 58: 233–238

[315] Suryanarayanan TS, Thirunavukkarasu N, Govindarajulu MB, Gopalan V. Fungal endophytes: an untapped source of biocatalysts. Fungal Divers 2012; 54: 19–30

[316] Li X, He X, Hou L, Ren Y, Wang S, Su F. Dark septate endophytes isolated from a xerophyte plant promote the growth of *Ammopiptanthus mongolicus* under drought condition. Sci Rep 2018; 8: 7896

[317] Jogawat A, Vadassery J, Verma N, Oelmüller R, Dua M, Nevo E, Johri AK. PiHOG1, a stress regulator MAP kinase from the root endophyte fungus *Piriformospora indica*, confers salinity stress tolerance in rice plants. Sci Rep 2016; 6: 36765

[318] Mastan A, Bharadwaj R, Kushwaha RK, Vivek Babu CS. Functional fungal endophytes in *Coleus forskohlii* regulate labdane diterpene biosynthesis for elevated forskolin accumulation in roots. Microb Ecol 2019. doi:10.1007/s00248-019-01376-w

[319] Kushwaha RK, Singh S, Pandey SS, Kalra A, Babu CSV. Fungal endophytes attune withanolide biosynthesis in *Withania somnifera*, prime to enhanced withanolide A content in leaves and roots. World J Microbiol Biotechnol 2019; 35: 20

[320] Ray T, Pandey SS, Pandey A, Srivastava M, Shanker K, Kalra A. Endophytic consortium with diverse gene-regulating capabilities of benzylisoquinoline alkaloids biosynthetic pathway can enhance endogenous morphine biosynthesis in *Papaver somniferum*. Front Microbiol 2019; 10: 925

[321] Rajagopal K, Suryanarayanan TS. Isolation of endophytic fungi from leaves of neem (*Azadirachta indica* A. Juss.). Curr Sci 2000; 78: 1375–1378

[322] Wilson D, Carroll GC. Infection studies of *Discula quercina*, an endophyte of *Quercus garryana*. Mycologia 1994; 86: 635–647

[323] Mahesh B, Tejesvi MV, Nalini MS. Endophytic mycoflora of inner bark of *Azadirachta indica* A. Juss. Curr Sci 2005; 88: 218–219

[324] Verma VC, Singh SK, Prakash S. Bio-control and plant growth promotion potential of siderophore producing endophytic Streptomyces from *Azadirachta indica* A. Juss. J Basic Microbiol 2011; 51: 550–556

[325] Shao S, Wu S, Chen Y, Wang L, Yang L, Li S, Li Z. Composition of endophytic fungi in *Azadirachta indica* from Yuanjiang County of Yunnan. Biodivers Sci 2008; 16: 63–67

[326] Tenguria RK, Khan FN. Distribution of endophytic fungi in leaves of *Azadirachta indica* A. Juss. (Neem) of Panchmarhi Biosphere Reserve. Curr Bot 2011; 2: 27–29

[327] Verma VC, Gond SK, Mishra A, Kumar A, Kharwar RN. Selection of natural strains of fungal endophytes from *Azadirachta indica* A. Juss, with antimicrobial activity against dermatophytes. Curr Bioact Compd 2008; 4: 36–40

[328] Gohain A, Gogoi A, Debnath R, Yadav A, Singh BP, Gupta VK, Sharma R, Saikia R. Antimicrobial biosynthetic potential and genetic diversity of endophytic actinomycetes associated with medicinal plants. FEMS Microbiol Lett 2015; 362: fnv158

[329] Kuncharoen N, Kudo T, Ohkuma M, Tanasupawat S. *Micromonospora azadirachtae* sp. nov., isolated from roots of *Azadirachta indica* A. Juss. var. siamensis Valeton. Antonie Van Leeuwenhoek 2019; 112: 253–262

[330] Stierle A, Strobel G, Stierle D. Taxol and taxane production by *Taxomyces andreanae*, an endophytic fungus of Pacific yew. Science 1993; 260: 214–216

[331] Strobel GA, Miller RV, Miller C, Condron M, Teplow DB, Hess WM. Cryptocandin, a potent antimycotic from the endophytic fungus *Cryptosporiopsis cf. quercina*. Microbiology 1999; 145: 1919–1926

[332] Li JY, Strobel GA, Harper JK, Lobkovsky E, Clardy J. Cryptocin, a potent tetramic acid antimycotic from the endophytic fungus *Cryptosporiopsis cf. quercina*. Org Lett 2000; 2: 767–770

[333] Li JY, Harper JK, Grant DM, Tombe BO, Bashyal B, Hess WM, Strobel GA. Ambuic acid, a highly functionalized cyclohexenone with antifungal activity from *Pestalotiopsis* spp. and *Monochaetia* sp. Phytochemistry 2001; 56: 463–468

[334] Ding G, Li Y, Fu S, Liu S, Wei J, Che Y. Ambuic acid and torreyanic acid derivatives from the endolichenic fungus *Pestalotiopsis* sp. J Nat Prod 2009; 72: 182–186

[335] Lee JC, Yang X, Schwartz M, Strobel G, Clardy J. The relationship between an endangered North American tree and an endophytic fungus. Chem Biol 1995; 2: 721–727

[336] Li JY, Strobel GA. Jesterone and hydroxy-jesterone antioomycete cyclohexenenone epoxides from the endophytic fungus *Pestalotiopsis jesteri*. Phytochemistry 2001; 57: 261–265

[337] Brady SF, Wagenaar MM, Singh MP, Janso JE, Clardy J. The cytosporones, new octaketide antibiotics isolated from an endophytic fungus. Organic Lett 2000; 14: 4043–4046

[338] Singh MP, Janso JE, Brady SF. Cytoskyrins and cytosporones produced by cytospora sp. CR200: taxonomy, fermentation and biological activities. Mar Drugs 2007; 5: 71–84

[339] Lee JC, Strobel GA, Lobkovsky E, Clardy JC. Torreyanic acid: a selectively cytotoxic quinone dimer from the endophytic fungus *Pestalotiopsis microspora*. J Org Chem 1996; 6: 13232–13233

[340] Zhang LQ, Guo B, Li HY, Zeng SR, Shao H, Gu S, Wei RC. Preliminary study on the isolation of endophytic fungus of *Catharanthus roseus* and its fermentation to produce products of therapeutic value. Chinese Traditional Herbal Drugs 2000; 31: 805–811

[341] Zhang LQ, Wang HK, Shao H, Shen YM, Zeng SR, Xu CD, Xuan Q, Wei RC. Isolation and determination of the anti-cancer substance of chaetoglobosin A producing by endophytic fungus of *Maytenus hookeri* (in Chinese). Chinese Pharma J 2002; 37: 172–175

[342] Lin ZJ, Lu ZY, Zhu TJ, Fang YC, Gu QQ, Zhu WM. Penicillenols from *Penicillium* sp. GQ-7, an endophytic fungus associated with *Aegiceras corniculatum*. Chem Pharm Bull 2008; 56: 217–221

[343] Kusari S, Zühlke S, Spiteller M. An endophytic fungus from *Camptotheca acuminata* that produces camptothecin and analogues. J Nat Prod 2009; 72: 2–7

[344] Harper JK, Ford EJ, Strobel GA, Arif AM, Grant DM, Porco JA jr., Tomer DP, Oneill KK. Pestacin (I): a 1,3-dihydro isobenzofuran from *Pestalotiopsis microspora* possessing antioxidant and antimycotic activities. Tetrahedron 2003; 59: 2471–2476

[345] Strobel GA, Ford E, Worapong J, Harper JK, Arif AM, Grant DM, Fung PCW, Chan K. Ispoestacin, an isobenzofuranone from *Pestalotiopsis microspora*, possessing antifungal and antioxidant activities. Phytochemistry 2002; 60: 179–183

[346] Lee J, Lobkovsky E, Pliam NB, Strobel GA, Clardy J. Subglutinols A and B: immunosuppressive compounds from the endophytic fungus *Fusarium subglutinans*. J Org Chem 1995; 60: 7076–7077

[347] Singh SB, Zink DL, Guan Z, Collado J, Pelaez F, Felock PJ, Hazuda DJ. Isolation, structure, and HIV-1 integrase inhibitory activity of xanthoviridicatin E and F, two novel fungal metabolites produced by *Penicillium chrysogenum*. Helvetica Chimica Acta 2003; 86: 3380–3385

[348] Tan RX, Zou WX. Endophytes: a rich source of functional metabolites. Nat Prod Rep 2001; 18: 448–459

[349] Kharwar RN, Mishra A, Gond SK, Stierle A, Stierle D. Anticancer compounds derived from fungal endophytes: their importance and future challenges. Nat Prod Rep 2011; 28: 1208–1228

[350] Chutulo EC, Chalannavar RK. Endophytic mycoflora and their bioactive compounds from *Azadirachta indica*: a comprehensive review. J Fungi (Basel) 2018; 4: E42

[351] Kusari S, Hertweck C, Spiteller M. Chemical ecology of endophytic fungi: origins of secondary metabolites. Chem Biol 2012; 19: 792–798

[352] Li GH, Yu ZF, Li X, Wang XB, Zheng LJ, Zhang KQ. Nematicidal metabolites produced by the endophytic fungus *Geotrichum* sp. AL4. Chem Biodivers 2007; 4: 1520–1524

[353] Wu SH, Chen YW, Shao SC, Wang LD, Li ZY, Yang LY, Li SL, Huang R. Ten-membered lactones from *Phomopsis* sp., an endophytic fungus of *Azadirachta indica*. J Nat Prod 2008; 71: 731–734

[354] Wu SH, Chen YW, Shao SC, Wang LD, Yu Y, Li ZY, Yang LY, Li SL, Huang R. Two new solanapyrone analogues from the endophytic fungus *Nigrospora* sp. YB-141 of *Azadirachta indica*. Chem Biodivers 2009; 6: 79–85

[355] Wu SH, Chen YW, Shao SC, Li ZZ, Yang LY, Li SL. Studies on the metabolites of *Aspergillus aculeatus* YM 311498, an endophytic fungus from *Azadirachta indica* A. Juss. Nat Prod Res Dev 2009; 21: 731–732

[356] Garcia-Sosa K, Villarreal-Alvarez N, Lubben P, Peña-Rodriguez LM. Chrysophanol, an antimicrobial anthraquinone from the root extract of *Colubrina greggii*. J Mex Chem Soc 2006; 50: 76–78

[357] Kupchan SM, Karim A. Tumor inhibitors. 114. Aloe emodin: antileukemic principle isolated from *Rhamnus frangula* L. Lloydia 1976; 39: 223–224

[358] Kusari S, Lamshöft M, Zühlke S, Spiteller M. An endophytic fungus from *Hypericum perforatum* that produces hypericin. J Nat Prod 2008; 71: 159–162

[359] Wu SH, Chen YW, Miao CP. Secondary metabolites of endophytic fungus *Xylaria* sp. YC-10 of *Azadirachta indica*. Chem Nat Comp 2011; 47: 858–861

[360] Boonphong S, Kittakoop P, Isaka M, Pittayakhajonwut D, Tanticharoen M, Thebtaranonth Y. Multiplolides A and B, new antifungal 10-membered lactones from *Xylaria* multiplex. J Nat Prod 2001; 64: 965–967

[361] Alam SS, Bilton JM, Slawin MZ, Williams DJ, Sheppard RN, Strange RM. Chickpea blight: production of the phytotoxins solanapyrones A and C by *Ascochyta rabiei*. Phytochemistry 1989; 28: 2627–2630

[362] Hohl B, Weidemann C, Hohl U, Barz W. Isolation of solanapyrones A, B and C from culture filture and spore germination fluids of *Ascochyta rabiei* and aspects of phytotoxin action. J Phytopathol 1991; 132: 193–206

[363] Latif Z, Strange RN, Bilton J, Riazuddin S. Production of the phytotoxins, solanapyrones A and C and cytochalasin D among nine isolates of *Ascochyta rabiei*. Plant Pathol 1993; 42: 172–180

[364] Ichihara A, Tazaki H, Sakamura S. Solanapyrones A, B and C, phytotoxic metabolites from the fungus *Alternaria solani*. Tetrahedron Lett 1983; 24: 5373–5376

[365] Oikawa H, Yokota T, Sakano C, Suzuki Y, Naya A, Ichihara A. Solanapyrones, phytotoxins produced by *Alternaria solani*: biosynthesis and isolation of minor components. Biosci Biotechnol Biochem 1998; 62: 2016–2022

[366] Jenkins KM, Toske SG, Jensen PR, Fenical W. Solanapyrones E–G, antialgal metabolites produced by a marine fungus. Phytochemistry 1998; 49: 2299–2304

[367] Wu SH, He J, Li XN, Huang R, Song F, Chen YW, Miao CP. Guaiane sesquiterpenes and isopimarane diterpenes from an endophytic fungus Xylaria sp. Phytochemistry 2014; 105: 197–204

[368] Huang R, Xie XS, Fang XW, Ma KX, Wu SH. Five new guaiane sesquiterpenes from the endophytic fungus Xylaria sp. YM 311647 of *Azadirachta indica*. Chem Biodivers 2015; 12: 1281–1286

[369] Chatterjee S, Ghosh R, Mandal NC. Production of bioactive compounds with bactericidal and antioxidant potential by endophytic fungus *Alternaria alternata* AE1 isolated from *Azadirachta indica* A. Juss. PLoS One 2019; 14: e0214744

[370] Verma VC, Kharwar RN, Gange AC. Biosynthesis of antimicrobial silver nanoparticles by the endophytic fungus *Aspergillus clavatus*. Nanomedicine (Lond) 2010; 5: 33–40

[371] Kumar J, Sharma VK, Singh DK, Mishra A, Gond SK, Verma SK, Kumar A, Kharwar RN. Epigenetic activation of antibacterial property of an endophytic *Streptomyces coelicolor* strain azra 37 and identification of the induced protein using MALDI TOF MS/MS. PloS One 2016. doi:10.1371/journal.pone.0147876

[372] Berdy J. Thoughts and facts about antibiotics: where we are now and where we are heading. J Antibiot 2012; 65: 385–395

[373] Tejesvi VM, Mahesh B, Nalini MS, Prakash HS, Kini KR, Subbiah V, Shetty HS. Fungal endophyte assemblages from ethnopharmaceutically important medicinal trees. Can J Microbiol 2006; 52: 427–435